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Prevalence, causes and treatments of allergic rhinitis in Malaysia: a literature review

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Abstract

Recently, allergic rhinitis (AR) cases have been surging rapidly in many developing countries. However, the prevalence, risk factors and treatment modalities for AR within the Malaysian population have not been thoroughly evaluated. The present study aimed to provide a complete review of literature on allergic rhinitis in Malaysia. Available data indicated that the prevalence of AR varied across different age groups and regions in Malaysia, but there is an increasing trend among the younger population. The key contributing factor is exposure and sensitization towards several airborne allergens, mainly house dust mites, cat fur and fungi, with possible genetic predispositions. In addition, variations in the symptom severity may be associated with racial orientations. For management of the disease, standard prescriptions of conventional drugs (antihistamines, intranasal corticosteroids and nasal decongestants) remain as the treatment of choice. A small proportion of the native residents tend to resort to alternative approaches of self-healing through aromatherapy and natural food consumption such as tiger's milk mushroom and *Tualang* honey. In conclusion, the increase in the cases of AR in Malaysia is due to environmental and genetic factors which requires proper medical intervention as treatment strategies. The utilization of holistic approaches requires further studies and clear understanding prior to their integration into the standard of care. There are still many gaps in the knowledge and management of allergic rhinitis which demands further attention from the research community.

Keywords: Allergic rhinitis, Epidemiology, Causality, Genetic predisposition, Therapeutics

Background

Allergic rhinitis (AR), a type 1 hypersensitivity disorder, causes inflammation of the upper nasal cavity due to inappropriate immunologic reactions against harmless agents [1]. The cardinal symptoms of AR are sneezing, rhinorrhoea, nasal itchiness and congestion [2], sometimes accompanied with itchy and watery eyes [3–5]. Apart from the clinical burden, other implications of AR include sleep deprivation, absenteeism from school/work and lack of productivity [6, 7]. In 2018 alone, about US $30.7 to 105.4 billion were spent on treating AR within Asia-Pacific [6]. These reports insinuated that allergic rhinitis is a vexing form of allergy with multiple adverse repercussions. The global prevalence of AR stands at 15–25%, with children and adolescents more prone to this condition than adults [8]. Lately, significant rises in the disease epidemiology rates were noted in many countries [9–11]. In Malaysia, several studies were performed to assess the disease burden [4, 5, 12], but changes in the incidence rates of allergic rhinitis through the years within this population have not been clearly elucidated.

The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines have highlighted indoor (house dust mites, cockroaches, and animal dander) and outdoor (pollens and moulds) allergens as two of the most prominent causes of AR [13]. Nonetheless, other predisposing factors including family history of allergies and the presence of concurrent asthma and/or eczema may also be instrumental [14]. For the Malaysian scene, though there is a cornucopia of research carried out on the context of allergen sensitization for years, studies

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assessing the aetiologies of AR are still lacking. Usually, conventional medications are recommended as treatment option, but these are mainly for mitigation of symptom severities only. In this regard, the consumption of natural food sources such as honey, tiger's milk mushroom and *Kecubung* fruit, as employed by the local Malay population to counteract the effects of allergic rhinitis, are exceedingly unique yet disputable [15–17]. In spite of that, the potential therapeutic benefits of such treatments cannot be cast aside entirely and warrants further investigation.

Allergies have significant socioeconomic impacts on the lives of the sufferers; therefore, a good knowledge, attitude and practice towards AR is needed for long-term disease prevention. Unfortunately, a lack of awareness and understanding of allergic diseases among Malaysians has led to poor choice of treatment strategies [18], which caused improper management of symptoms and brought unnecessary costs to the patients. In this case, a thorough assessment of the situation of AR in Malaysia based on existing knowledge and practices is highly essential for resolution of this disease. With that, the current study attempts to describe the trend in the prevalence of AR in Malaysia and to identify causative agents responsible for AR in this population. In addition, we have also reviewed different types of treatment options available for AR in Malaysia. The final objective of this study is to identify gaps in the literature on allergic rhinitis-related studies in Malaysia and make relevant suggestions for future research opportunities.

The data for this review was collected from previously published literatures in the PubMed and Scopus databases. The following keywords were used to filter and extract relevant research articles: allergic rhinitis, hay fever, prevalence, epidemiology, causes, aetiology, treatment, therapy, Malaysia. The resulting papers were classified into three major subcategories: prevalence, aetiology (environmental and genetic factors) and treatment options (standard and traditional medications). For each of those categories, any or all information pertaining to AR in Malaysia were summarized, compiled and presented in the form of either figures or tables. As a mean to provide additional perspective to the subject matter, this paper has also included reviews of related international studies conducted primarily in the Asia-Pacific region. Discussion based on studies of other respiratory disorders such as asthma and atopic dermatitis was kept to a bare minimum unless deemed necessary, depending on the context of the topic. This is an initial comprehensive study dedicated to compile, analyse and present information on the prevalence, causes and treatments of allergic rhinitis in Malaysia.

Prevalence of allergic rhinitis in Malaysia

According to a multi-national survey by Katelaris et al. (2011), approximately 8.7% of the population across the Asia-Pacific region suffered from allergic rhinitis [19]. In that same survey, the prevalence rate of AR for Malaysia was estimated to be 7.1%, which was higher than other Southeast Asian countries such as Hong Kong, the Philippines and Singapore [19, 20].

Prevalence of allergic rhinitis in children

To date, many studies have reported on the prevalence of respiratory-related diseases in various regions (Fig. 1) throughout Malaysia. An earlier Southeast Asian population-based study evaluating the status of respiratory diseases among secondary school students in East Malaysia had established the prevalence of AR of 11.2% [3]. Another questionnaire-based survey administered to secondary school children from the East Coast showed the prevalence of AR at 11.0% and 14.8% in 1995 and 2001, respectively [4]. In 2016, the prevalence of AR was at 18.8% as presented by a survey involving 462 students from 8 secondary schools within the southern region of Peninsular Malaysia [5]. As of 2020, approximately 31.7% and 55.5% of junior high school students from the East Coast and central regions of Malaysia, respectively, had symptoms of AR [12, 21]. Direct comparison of epidemiologic rates from these studies indicates that the prevalence of AR has increased markedly over the years among secondary school children in Malaysia (Fig. 2). In one primary school in the central area, about 11.2% of the students aged between 7 and 12 years old were reported to have current rhinitis [22], whereas in the East Coast, a slight increase (+0.4%) in the occurrence of AR among primary school children was seen between 1995 and 2001 [4]. The International Study of Asthma and Allergies in Childhood (ISAAC) observed small increases in the incidence of AR among children (6 to 7 years old) and young teenagers (13 to 14 years old) in all of these regions (northern, central, East Coast and southern) between 1994 and 2002 (Table 1). During this same timeframe, a decrease in the prevalence rate of allergic rhinitis was only seen among teenagers from the northern region of Peninsular Malaysia (Table 1).

Prevalence of allergic rhinitis in young adults

In a cross-sectional study by Kumar et al. (2020), the prevalence of AR among 1000 higher education students (18 to 26 years old) was at 79.5%. Of this group, only 12.5% exhibited symptoms of AR since childhood [24]. There are, however, no other prevalence studies available for this age group in Malaysia.

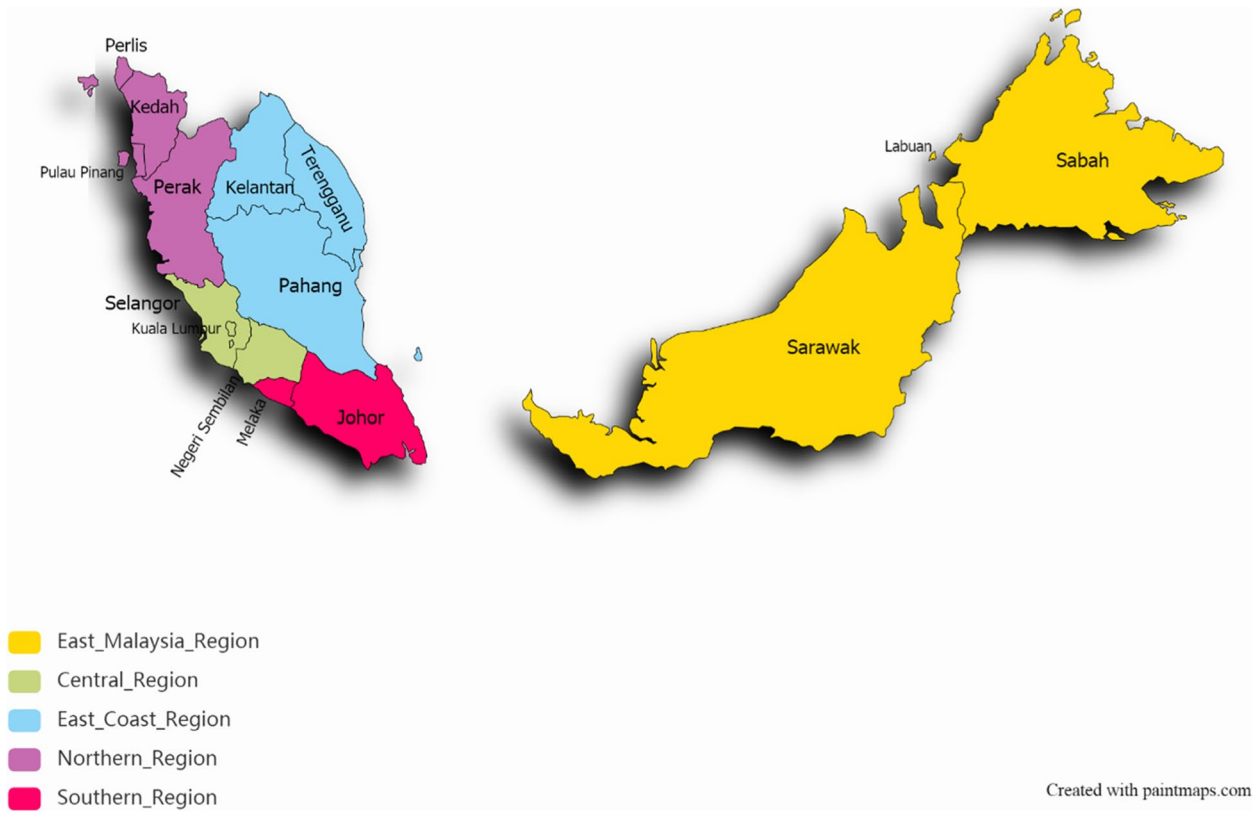

Fig. 1 Major geographical regions of Malaysia

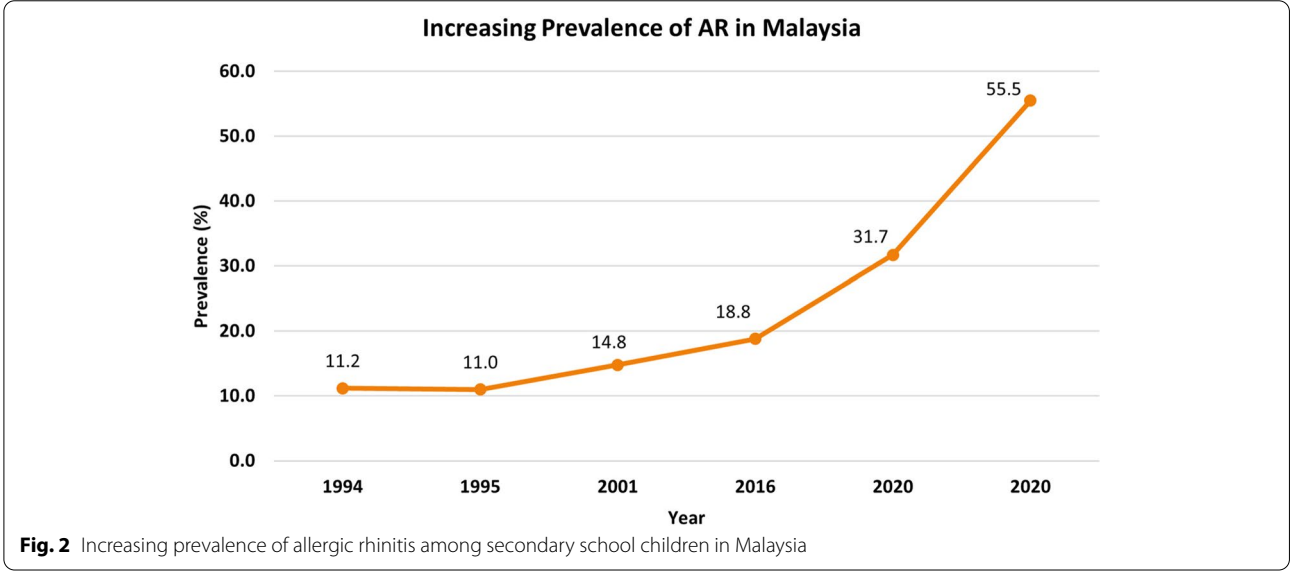

Fig. 2 Increasing prevalence of allergic rhinitis among secondary school children in Malaysia

Prevalence of allergic rhinitis in adults

For the Malaysian adult population, Lim et al. (2015) estimated the prevalence of AR to be about 53.0% [25]. The findings of this study were limited to office workers from a random tertiary education centre in the central region of Peninsular Malaysia only and were not indicative of the population at large due to differences in occupational backgrounds, age groups, racial profiles and gender.

Table 1 Trends in the epidemiology of allergic rhinitis among Malaysian children and young teenagers based on the results of the ISAAC survey

Prevalence rate (%)						
Age group	**6–7 years old (children)**			**13–14 years old (teenagers)**		
Region	**Phase I**	**Phase III**	**Change**	**Phase I**	**Phase III**	**Change**
Northern	3.6	4.2	+0.6	16.7	16.3	−0.4
Northern	4.6	-	-	18.0	-	-
Central	5.0	6.2	+1.2	14.6	19.8	+5.2
East Coast	3.8	4.2	+0.4	9.6	12.5	+2.9
Southern	2.8	-	-	8.0	-	-
Average	4.0	4.9	0.9	13.4	16.2	+2.8

The International Study of Asthma and Allergies in Childhood (ISAAC) was conducted in three separate time frames, namely phase I (1994–1995), phase II (1998) and phase III (2001–2002), respectively [23]. Malaysia was part of phases I and III of the study. (-) indicates data not available

Under these circumstances, it would be of great benefit to have more AR epidemiological studies performed systematically at nationwide scales to obtain a better representation of the general Malaysian population.

Environmental agents associated with allergic rhinitis in Malaysia

House dust mites Studies from the Middle East, Europe and Southeast Asia emphasized that allergic sensitization to house dust mites contributes tremendously towards allergic rhinitis development [26–28], and Malaysia is of no exception [25]. Previously, Mariana et al. (2000) showed that Malaysian households were heavily infested with house dust mites [29] These mites survive and reproduce more readily in tropical weather countries, owing to the favourable environmental temperatures and humidity levels that facilitate their growth and developmental cycles [30]. This explains their relative abundance within the local communities, particularly in the urban and suburban areas [29]. Three of the most common species of dust mites that can trigger significant reactivities among Malaysians are *Dermatophagoides pteronyssinus* (European house dust mite), *Dermatophagoides farinae* (American house dust mite) and *Blomia tropicalis* (Table 2). Yadav et al. (2015) made an interesting observation in their cross-sectional study of AR, whereby children aged between 2 and 10 years old had significantly higher sensitization rates towards *D. pteronyssinus* and *B. tropicalis* than infants younger than 2 years old [39] (Table 2). This implies that exposure to risk factors begins during early childhood stages, and this sensitization process persists and develops rapidly into the later years. As such, longitudinal studies are necessary to investigate the impacts of childhood allergen introduction on the occurrence of allergic rhinitis.

Cat fur Certain types of mammalian-derived allergens including fur, dander (skin flakes), feather and saliva from domesticated pets and farm animals might trigger allergic rhinitis [41]. According to Pang et al. (2017), most Asian AR patients were sensitized towards airborne allergens from cats (19.0%) and dogs (32.0%) [42]. This agrees with the findings of Yadav and Naidu (2013) that children with AR were more likely to own pets at their homes [43]. Data from several studies assert that cat allergy is the second most important AR inducing factor after common dust mites in Malaysia [31, 34, 35], with an estimated prevalence of 25.4% among urban office workers [25]. Cats secrete an allergenic glycoprotein, Fel d 1, from sebaceous gland under their skin and fur which can stimulate Th2-driven hypersensitivities in humans upon inhalation/ingestion [44]. This allergen usually resides on upholstered furniture in homes with cat ownership; nonetheless, it can also be found in considerable amounts on car seats and school floors [45]. Norbäck et al. (2016) showed that the Fel d 1 allergen was consistently present in settled dust samples collected from classrooms of selected schools in the southern region of Malaysia [5]. Further studies relating varying concentrations of Fel d 1 at different sampling sites are needed as they may shed some light on deciphering the threshold level required for initiation of allergen-specific sensitization.

Fungi Fungi are another typically implicated airborne immunogen after dust mites and animal dander [8]. Recent research had established significant positive association between levels of total fungal DNA in settled dust and rhinitis symptoms among Malaysian students [5]. Furthermore, Fu et al. (2020) demonstrated that fungal richness in school classrooms was positively correlated with allergic rhinitis [21]. Early childhood exposure to high concentrations of fungal allergens may lead

Table 2 Summary of skin prick tests and serum IgE tests among mite-induced allergies in different regions of Malaysia

Region of study	Sample size	Patient demographics	Type of mites tested and their reactivities (%)		References
			Skin prick test	Serum IgE test	
East Malaysia	321	High school students. Chinese only (100%)	*D. pteronyssinus* (60.5)	-	Leung and Ho (1994) [3]
Central	316	> 7 years old With AR only	*D. pteronyssinus* (82.0) House dust (81.0)	-	Ho et al. (1995) [31]
Central	90	6–50 years old With AR only	-	*D. pteronyssinus* (79.0) *D. farinae* (78.0)	Kook & Soong (1995) [32]
Central	148	> 17 years old With AR only	House dust mites (66.8) *D. pteronyssinus* (72.3) *D. farinae* (50.6)	-	Gendeh et al. (2000) [33]
Central	141	0–12 years old With AR only	House dust mites (69.5)	-	Gendeh et al. (2004) [34]
East Coast	90	18–66 years old With AR only	House dust mites (80.0)	-	Asha'ari et al. (2010) [35]
Central	580	5–12 years old With AR only	*D. pteronyssinus* (63.9) *D. farinae* (60.4) *B. tropicalis* (59.7)	-	Zahedi et al. (2011) [36]
Northern	100	> 18 years old With & without AR Chinese majority (70.0%)	-	*D. farinae* (35.0) *Glycycometus malaysiensis* (37.0)	Chong et al. (2015) [37]
Central	463	18–59 years old Malay majority (97.8%)	*D. pteronyssinus* (50.3) *D. farinae* (49.0)	-	Lim et al. (2015) [25]
Central	102	0–84 years old With AR only	*D. pteronyssinus* (78.4) *D. farinae* (77.5) *Blomia* sp. (69.0)	-	Nadzrah et al. (2015) [38]
Central	192	< 2 years old (35 children) 2–10 years old (157 children) With allergies	-	< 2 years old *D. pteronyssinus* (23.1) *B. tropicalis* (16.7) 2–10 years old *D. pteronyssinus* (63.3) *B. tropicalis* (63.2)	Yadav & Naidu (2015) [39]
Northern	93	18–60 years old Atopic population	House dust mites (78.5)	-	Kttafah et al. (2020) [40]
Central	470	14 years old only High school students With and without AR	*D. pteronyssinus* (51.9) *D. farinae* (47.9)	-	Mohd Isa et al. (2020) [12]

to sensitization, and this depends heavily on the age of first contact as well as the strain involved [46]. In Thailand, the three main species of fungi that caused positive reactions among rhinitis patients were *Cladosporium* sp., *Penicillium* sp. and *Aspergillus* sp [47]. Interestingly, a different pattern of sensitization was seen among Malaysian subjects, with the prevalence of 23.5%, 21.2% and 18.8% for *Fusarium* sp., *Aspergillus flavum* and *Dreselera orysae*, respectively [48]. In addition, Kttafah et al. (2020) observed the greatest number of positive responses towards *Aspergillus fumigatus* in their study of fungal sensitization among Malaysian atopic populations [40]. This disparity in sensitization between Thailand and Malaysia might be due to variations in the fungal spore distribution in both countries, which in turn are strongly affected by climatic parameters such as rainfall and humidity levels [47]. In this case, multicentre birth cohort studies might be useful in understanding the correlation that exist between fungi strain, meteorological conditions and allergic rhinitis predisposition.

Bacteria and associated biomarkers Indoor microbiome exposure may exert some influence on the occurrence of allergic rhinitis in Malaysia. According to Fu et al. (2020), Gammaproteobacteria, Cyanobacteria and Deinococci, among a few others, were some of the most abundant classes of bacteria found within school classrooms in the East Coast of Malaysia [21]. The richness in the class, Gammaproteobacteria, was significantly, protectively associated with AR, while *Aeromonas enteropelogenes*, *Escherichia fergusonii* and *Brasilonema bromeliae* were negatively associated with AR. On the contrary, *Deinococcus grandis* was positively correlated with AR

[21]. This could mean that exposure to certain types of bacteria may lead to either predisposition or protection against AR. However, due to limitation of studies in this area, the exact role of microorganisms in the pathogenesis of AR remains to be seen.

In some cases, chemical microbial markers may also contribute towards development of rhinitis symptoms. Norbäck et al. (2016) showcased that exposure to endotoxins with C14 3-hydroxy fatty acid (3-OH FA) group was positively correlated with the incidence of AR among Malaysian high school students [49]. Endotoxins or lipopolysaccharides (LPS) are biochemical structures that form part of the outer surface of the cell membrane of a gram-negative bacterium, which upon its lysis can trigger potent activation of the immune system [50]. Braga et al. (2004) demonstrated that simultaneous inhalation of lipopolysaccharides and *D. pteronyssinus* allergen extract can greatly intensify the nasal allergic reactions as opposed to that of single antigenic challenges alone [51]. Moreover, elevated levels of lipopolysaccharides in the environment were linked with higher occurrence of AR [52]. These findings support the idea that bacterial-derived biomarkers can act as mediators in the pathomechanism of allergic disorders. Future assessment should focus more on investigating the interrelationship between endotoxin polymorphisms and their associated effects on allergic rhinitis manifestation.

Genetic predisposition of allergic rhinitis in Malaysia

Over the past three decades, various studies have suggested noteworthy correlations between specific determinants such as stress levels, family income and daily computer usage time with the epidemiology of AR throughout Asia [20]. One of the most important risk factor that is strongly linked with AR predisposition is an individual's genetic makeup. Genome-wide association studies (GWAS) and next-generation sequencing techniques have allowed for precise locating of genes susceptible for allergic disorders [53]. A recently conducted meta-analysis in a European population had pinpointed several major histocompatibility complex (MHC) genes that can confer high susceptibility to allergic rhinitis which include *HLA-B*, *HLA-DQA1*, *HLA-DQA2* and *HLA-DRB1* [54]. In a review by Spinola (2017), the linkage between human leukocyte antigen (HLA) genes and AR seemed to vary depending on the effect of the gene (protective or predisposing), population under study and type of allergen sensitization [55]. For instance, *HLA-DQB1*06:01:01* and *HLA-DRB1*08:03:02* were considered as risk alleles for HDM-sensitized AR, whereas *HLA-DQB1*05* conferred protection in a Chinese Han ethnic group [56]. Likewise, alleles *HLA-DPB1*05:01* and *HLA-DPB1*02* conveyed susceptible and protective roles, respectively, among Japanese rhinitis subjects with cedar pollinosis and sensitization [57].

The distribution of HLA class I and II allelomorphs in Malaysia varies considerably across different racial groups and aboriginal tribes. Malaysia is comprised of three major ethnic groups, namely Malays, Chinese and Indians. The Malays shared many HLA alleles, especially *A*24*, *B*15*, *Cw*04*, *Cw*07*, *DQB1*03*, *DQB1*05*, *DRB1*12* and *DRB1*15*, with other Malay sub-ethnic groups such as Banjar, Bugis, Jawa, Kelantan and Rawa (Table 3). Several of those variants were also prevalent among indigenous groups from East Malaysia; however, alleles *A*11*, *B*18*, *DRB1*09* and *DRB1*16* were more common within this population than in the Malays (Table 4). The Malaysian Chinese differed from the Malays in terms of alleles *B*40:01*, *C*01:02*, *DQB1*03:03* and *DRB1*09* (Table 4). Due to a lack of studies, comparison of HLA alleles for the Malaysian Indian population was not conducted in this review. Some of these HLA class I and II polymorphs were significantly linked with autoimmune and malignant disorders in Malaysia including systemic lupus erythematosus [68–70], rheumatoid arthritis [71], aplastic anaemia [72], and leukaemia [73]. Apart from that, two local studies had independently demonstrated a strong association between *HLA-B*15:02* allele and drug-induced (carbamazepine) hypersensitive reactions in patients and healthy controls, irrespective of their ancestries [74, 75]. However, studies on the interrelation between HLA markers and allergic predisposition in Malaysia are still lacking.

Besides the HLA genes, studies by Ramasamy et al. (2011) and Bønnelykke et al. (2013) indicated that certain loci harbouring genes such as *C11ORF30/EMSY*, *IL2*, *STAT6* and *TMEM232* contained different forms of intergenic single-nucleotide polymorphisms (SNPs) that significantly increased the risk of developing AR through allergen-specific sensitizations [76, 77]. Andiappan et al. (2011) had reported two novel SNPs in *MRPL4* and *BCAP* gene loci, respectively, which might act as risk candidates for rhinitis among Singaporean Chinese population [78]. Within Chinese Han community, AR risk variants were seen near *EMSY-LRRC32* locus, whereas a protective genotype was found at *IL4* region [79]. In Japan, two variants in *IL-1B* genomic stretch were determined to be associated with cedar and cypress allergy [80]. Similarly, a Malaysian pilot study by Yadav et al. (2013) established a significant relationship between a variant of *IL-13* gene (IL-13 R130Q) and allergic rhinitis development [81], thereby affirming that SNPs play a huge role in the pathomechanism of allergic diseases. The potential role of these genes should be further confirmed

Table 3 Common HLA alleles among Malays and their sub-ethnic groups in Malaysia

Ethnic groups	Common HLA alleles					References
	HLA-A	HLA-B	HLA-C	HLA-DQ	HLA-DR	
Malay	A*02 A*11(:01) A*24(:02)	B*15(:02)	Cw*03 Cw*04 Cw*07 C*08:01	DQA1.2 DQA4.0 DQB1*03(:01) DQB1*05(:02) DQB1*07 DQB1*08	DRB1*12(:02) DRB1*15(:02)	Dhaliwal et al. (2007) [58] Azira et al. (2013) [59] Edinur et al. (2009) [60] Tan et al. (2016) [61] Koh & Benjamin (1994) [62]
Banjar, Bugis and Jawa	A*02 A*24	B*15 B*35	Cw*03 Cw*04 Cw*07 Cw*08	DQB1*03 DQB1*05	DRB1*04 DRB1*12 DRB1*15	Edinur et al. (2009) [60]
Champa	A*11:01	B*15:02	-	-	DRB1*12:02 DRB1*15:02	Allia et al. (2019) [63]
Kelantan	A*11 A*24:02 A*24:07 A*33	B*15:02	Cw*04 Cw*07	DQB1*03 DQB1*05	DRB1*12(:02) DRB1*15	Allia et al. (2019) [63] Edinur et al. (2009) [60]
Mandailing	A*02:01 A*24:02	B*15:02 B*15:13	-	-	DRB1*12:02 DRB1*15:02	Allia et al. (2019) [63]
Minangkabau	A*11 A*24	B*15 B*18 B*35	Cw*04 Cw*07	DQB1*02 DQB1*03 DQB1*05	DRB1*07 DRB1*12 DRB1*15	Edinur et al. (2009) [60]
Patani	A*24:07 A*33:03	B*15:02 B*40:01 B*58:01	-	-	DRB1*12:02	Allia et al. (2019) [63]
Rawa	A*24	B*15	Cw*03 Cw*04 Cw*07	DQB1*02 DQB1*03 DQB1*05	DRB1*12	Edinur et al. (2009) [60]

via mechanistic studies and validated on a larger population size.

Ethnicity and allergic rhinitis

The latest version of the ARIA guidelines has classified AR based on duration (intermittent or persistent) and symptom severity (mild or moderate-severe) [13]. The degrees of AR symptoms intensity are predominantly controlled by circulating allergen-specific IgE levels [82], polysensitization status [83, 84], duration of allergy and the presence of comorbidities [85]. In some inflammatory disorders (SLE and ankylosing spondylitis), significant differences in the disease chronicity were noticed within the population when racial and ethnic backgrounds were factored in [86, 87]. This leads to the hypothesis that ethnicity can trigger variations in the symptom severities. Although the prevalence of allergic rhinitis among the Malays was lower than the non-Malays [43], Amini et al. (2016) inferred that the Malays were more likely to suffer from the most severe symptoms of AR [88]. On the contrary, the Chinese and Indians mainly experienced mild to moderate effects. The same study also supported the notion that elevation in disease severity among the Chinese and Indians depended more on the periods of concomitant allergic diseases, such as atopic dermatitis and asthma, rather than the duration of AR alone. The Indians, in particular, exhibited a positive association between polysensitivities and AR severity [88]. These results imply that ethnicity contributes towards exacerbation of nasal symptoms in relation to rhinitis. Future directions would be to study the involvement of other relevant variables such as genetic background and socioeconomic status, on the symptom severity between different races.

Management and treatment of allergic rhinitis in Malaysia

Two distinct modalities that are currently in practice are prevention of allergen contact and treatment with medical therapies [89].

Preventive self-care practices

In a review of house dust mites (HDM) in Malaysia by Nadchatram (2005), carpets and mattresses were listed as the primary habitats of *B. tropicalis* and *D. pteronyssinus*. Routine washing and high-temperature drying of clothes, bed sheets, pillowcases and carpets were essential in maintaining low levels of HDM and its associated allergens at homes [30]. For animal-based allergies, avoiding

Table 4 Common HLA alleles among non-Malays and various indigenous populations in Malaysia

Ethnic groups	Common HLA alleles					References
	HLA-A	HLA-B	HLA-C	HLA-DQ	HLA-DR	
Chinese	A*02:01 A*11:01 A*24:02	B*40:01	C*01:02 C*07:02	DQA3.0 DQA4.0 DQB1*03:01 DQB1*03:03 DQB1*05:02	DRB1*09:01	Too et al. (2019) [64] Koh & Benjamin (1994) [62]
Indian	-	-	-	DQA1.1 DQA1.3	-	Koh & Benjamin (1994) [62]
Bidayuh	A*11 A*24	B*15(:02) B*15(:21)	-	DQB1*03:G1 DQB1*05:02 DQB1*06:01	DRB1*12:02 DRB1*16:02	Dhaliwal et al. (2010) [65] Jinam et al. (2010) [66]
Iban	A*11 A*24(:07)	B*15	-	-	DRB1*12:02 DRB1*15:02	Dhaliwal et al. (2010) [65]
Jehai	A*24:07	B*18:01	-	DQB1*03:03 DQB1*05:01	DRB1*09:01 DRB1*15:02	Jinam et al. (2010) [66]
Kadazan	A*11 A*24 A*34	B*38 B*40	-	-	DRB1*04:05 DRB1*15:02	Dhaliwal et al. (2010) [65]
Kensiu	A*02:G1(:01) A*11:01 A*24:07	B*13:01 B*15:13 B*18:01	-	DQB1*03:03 DQB1*05:02	DRB1*09:01 DRB1*15:01	Jinam et al. (2010) [66] Tasnim et al. (2016) [67]
Semai	A*24:02 A*24:07	B*15:02 B*18:01	-	-	DRB1*12:02 DRB1*15:02 DRB1*16:02	Tasnim et al. (2016) [67]
Temuan	A*11:01 A*24:07	B*15:25 B*18:01	-	DQB1*03:G1 DQB1*05:02	DRB1*09:01 DRB1*16:02	Jinam et al. (2010) [66]

exposure to furry pets and its surroundings was highly advised [89]. In addition, the Malaysian Allergy Prevention (MAP) guidelines suggested that patients with allergic disorders may benefit from elimination/removal of HDM and pets; however, persons subjected to pets during early infancy may not be at risk for developing allergy [90].

Conventional treatment

Some of the most typically administered conventional drugs for treatment of allergic rhinitis in Malaysia are anti-histamines (e.g. cetirizine, chlorpheniramine, desloratadine and loratadine), intranasal corticosteroids (e.g. budesonide, fluticasone furoate and mometasone) and nasal decongestants (e.g. oxymetazoline) [91]. Loratadine and cetirizine were two of the most preferred choice of anti-histamines for AR management in several Southeast Asian countries [92]. Azelastine nasal spray is another typically prescribed anti-histamine with demonstrated excellence in its safety and efficacy profiles [93]. On the other hand, mometasone furoate and fluticasone furoate nasal sprays displayed equal efficacies as monotherapy for allergic rhinoconjunctivitis, as demonstrated by Aneeza et al. (2013) in a Malaysian population [94]. Additionally, Goh et al. (2014) showed that montelukast in combination with fluticasone propionate (nasal spray) helped to mitigate nasal-ocular symptoms and significantly improve the quality of life in a cohort of Malaysian patients with moderate to severe allergic rhinitis [95].

The ARIA guidelines suggested that the choice of treatment (monotherapy and/or combinatorial) for any group of patients must take into account several factors such as their ages, comorbidities, type of rhinitis (perennial or seasonal) and severity of symptoms [13]. These approaches, however, were mostly based on low certainties of experimental/clinical evidence and should be viewed as conditional recommendations only [13]. Even though the ARIA guidelines have been continuously revised and updated over the years, there exist a wide disparity in its perception and implementation at the primary care level. A recent survey of Malaysian physicians found that only 66.0% of general practitioners and medical officers were aware of the ARIA guidelines [96]. This is considerably lower than that seen in a previous cross-sectional study, which reported that 80.8% of general practitioners from four ASEAN countries (Thailand, Indonesia, Philippines and Malaysia) were well-informed of the ARIA guidelines [92]. In fact, only 58.0% of pharmacists and 66.0% of ENT specialists from Malaysia were satisfied with the suggestions outlined by ARIA, as reported by Prepageran et al. (2014) [97].

The diagnosis of allergic rhinitis in Malaysia is predominantly based on assessments of clinical history, followed by anterior rhinoscopy. Other practices such as allergy testing, imaging paranasal sinuses and nasal endoscopy are less commonly used [96]. Some of the preferred methods of allergy testing include skin prick test, skin patch test and blood serum analysis for total/specific IgE and eosinophil count [96]. Most Malaysian primary care physicians prioritized prescription of first- and second-generation oral anti-histamines and combination of oral anti-histamines with nasal decongestants for treatment of AR [96]. Similar choices were also favoured by most general practitioners and pharmacists from Indonesia, Philippines and Thailand [92]. For the treatment of mild AR, most Malaysian medical professionals preferred prescriptions of anti-histamines for a duration of less than 2 weeks, whereas a combination therapy of anti-histamines with intranasal steroids for more than 3 months was highly favoured by most local ENT specialists for moderate-severe cases of AR [97]. They also believed that efficacy is the most important criterion for selection of anti-histamine drugs. However, most general practitioners and ENT specialists were against increasing the doses of anti-histamines in the event of poor patient prognosis [97]. The ARIA guidelines, though greatly beneficial, lack some pertinent information on the use of anti-histamines, such as its maximum duration of treatment and acceptable levels of dosage increments for patients who are not responding favourably. As such, Abdullah et al. (2019) recommended patient profiling, on the basis of their age, gender and occupation, as a formal guide for prescription of anti-histamines in Malaysia, with follow-up actions taken to closely monitor patient responses thereafter [98].

Allergen immunotherapy

Immune-based therapies for specific allergens have shown promising results in averting the symptoms of allergic rhinitis [99]. In a single blind, randomized placebo-controlled trial, HDM-sensitized Chinese AR patients showed significant reductions in their mite sensitivities after oral consumption of encapsulated *D. farinae* allergen extract [100]. Fujisawa et al. (2018) also emphasized that subcutaneous injection of allergen mixture solution at appropriate doses provided long-term safety and efficacy among Japanese patients with HDM-induced AR [101]. Additionally, a research from Singapore found that sublingual intake of mite extract medication 'Staloral' can greatly improve the quality of AR patients' life by relieving nasal-associated symptoms [102]. As of yet, there has been no studies conducted on the effects of immunotherapies on allergic patients in Malaysia. Despite that, 'ACARIZAX', a form of sublingual immunotherapy (SLIT) tablet containing extracts of *D. pteronyssinus* and *D. farinae* allergens, was approved for marketing and distribution in several Southeast Asian countries, including Malaysia [103]. This tablet was shown to reduce the clinical symptoms of AR among European HDM-sensitized individuals with a lower expected risk of allergic reactions compared to subcutaneous immunotherapies (SCIT) [104]. Some of the most common adverse events related to oral-based immunotherapies were mild, inflammatory reactions around the mouth cavity and exacerbation of pre-existing rhinorrhoea; however, gastrointestinal effects were extremely rare in most cases [105].

Natural and alternative approaches

The Ministry of Health Malaysia has introduced policy statements to incorporate complementary and alternative medicine (CAM) therapies into its national healthcare system [106]. One baseline study by Siti et al. (2009) showed that herbs and herbal-based products were among some of the most extensively used medications by Malaysians for disease management [107].

Lignosus rhinocerotis, known locally as tiger's milk mushroom (*cendawan susu harimau*), is a naturally occurring medicinal fungus used frequently by the native populations for mitigation of respiratory symptoms due to its potent anti-inflammatory activities [16]. The therapeutic use of *L. rhinocerotis* extract (LRE) in the management of airway inflammation was investigated by Muhammad et al. (2019) using ovalbumin (OVA)-induced mouse model [108]. They observed significant reductions of eosinophils, lymphocytes, neutrophils and cytokines (IL-4 and IL-5) in the bronchoalveolar lavage fluid (BALF) as well as declination in total serum IgE levels upon intranasal administration of LRE with specific dosages for 7 consecutive days. Moreover, the authors also reported a decrease in the percentage of $CD4^+$ helper T cells in the lung-draining lymph nodes, including suppression of mucus secretion and leukocyte invasion in the lungs [108]. Johnathan et al. (2021) in their study of oral consumption of LRE on airway inflammation using OVA-induced rat models observed significant elevation of $CD4^+CD25^+Foxp3^+$ regulatory T cells in the BALF after treatment with LRE [109]. They also demonstrated down regulation of allergic/asthmatic-associated genes (*IL-17A* and *ADAM33*) following 7 days of *L. rhinocerotis* extract gavaging [109]. The preceding studies provided ample evidence on the in vivo effects of *L. rhinocerotis* in regulating the inflammatory mediators of allergy and asthma. Despite that, the murine models utilized in these studies were representative of allergic asthma only; hence, their findings might not be entirely conclusive for allergic rhinitis. Due to the small sample

sizes in both studies, the generalization of outcomes cannot be made as well.

Recently, a clinical prospective study by Tan et al. (2021) evaluated the efficacy of *L. rhinocerotis* intake on the improvement of health among a group of Malaysian volunteers [110]. The study participants orally consumed encapsulated, powdered form of *L. rhinocerotis*, twice daily, for 3 months, and follow-up visits after each month were conducted for examination of health status [110]. Increased levels of pulmonary functions and anti-oxidant capacities were observed with a huge reduction in respiratory symptoms as measured using validated nasal symptom questionnaire (NSQ) and visual analogue scale (VAS). Not only that, they also reported reduction in the levels of interleukins, IL-1β and IL-8 and elevation of salivary IgA levels [110]. Although seemingly promising, the lack of a placebo control group here made it difficult to assess the true efficacy of the supplement. Extended periods of treatment are also necessary to truly gauge the long-term effects of this extract. In addition, the specific contents of the supplement were not clearly mentioned, and only one type of dosage was used. There is also a strong potential for biasness due to the involvement of the supplier of *L. rhinocerotis* extract in this study.

Honey is another organic supplement taken regularly for its immunomodulatory effects. *Tualang* honey, produced by *Apis dorsata* (rock bee), is the most typically consumed honey in the practice of CAM within the central region of Malaysia [111]. The effect of *Tualang* honey on alleviation of airway-related symptoms was studied by Kamaruzaman et al. (2014) using ovalbumin (OVA)-induced asthmatic rabbit models. Upon treatment with aerosolized honey sprays for 5 days, marked attenuations in the levels of active eosinophils, macrophages and neutrophils were seen in the bronchoalveolar lavage fluid (BALF), alongside inhibitions of goblet cell hyperplasia in the lung airway lumens [112]. These findings provide sufficient initial evidence on the influence of *Tualang* honey in the management of asthma. The authors, however, did not disclose full information regarding the source and method of preparation of the aerosolized honey used in this study. No justifications were given on the use of only two concentrations of honey either. Future in vivo studies investigating the rescue and preventative effects of honey using murine models of AR will be useful in order to replicate the outcomes of the study by Kamaruzaman et al. (2014) in the nasal mucosa.

In a double-blinded, randomized-placebo controlled trial, Asha'ari et al. (2013) showed that oral ingestion of raw, unprocessed *Tualang* honey, in complementary with anti-histamine, could provide nasal symptom relief among Malaysian allergic rhinitis patients [15]. The placebo and treatment groups took 10 mg of loratadine for the first 4 weeks of the study, alongside honey-flavoured corn syrup (for placebo group only) and pure *Tualang* honey (for treatment group only). From weeks 5 until 8, the uptake of anti-histamine and the respective treatments were discontinued. At the end of the study, subjects from the treated group reported significant improvement in their nasal symptoms compared to the placebo group [15]. It should be taken into consideration that no laboratory assessment of serum total and specific IgE levels was performed during this study. Besides, clinical evaluation of nasal symptoms was not conducted during each follow-up as well. The short period of study and small sample size made it difficult to conclusively attribute the observed improvements to the intervention given.

Another randomized-controlled study by Abd Manab et al. (2018) investigated the potential role of *Tualang* honey as an adjunct therapy in the treatment of moderate to severe persistent allergic rhinitis [113]. The control and trial groups took intranasal corticosteroids and oral anti-histamines for a duration of 6 weeks, but only the trial group received an additional treatment of intranasal *Tualang* honey spray, taken daily at night throughout the same period. As a result, significant improvements in the symptom scores for nasal blockage, discharging and sneezing as well as reductions in total IgE levels were observed for both groups between weeks 0 and 6 of this study [113]. There was no significant difference between the control and trial groups for all of the parameters measured. Of note, the formulations used for preparation of the intranasal honey spray were well-described in this study. Unfortunately, this is non-blinded research wherein the trial group was pre-informed regarding the contents of the intranasal honey spray earlier on in the study. This might have created performance bias which could greatly affect interpretation of the data obtained. The lack of a proper placebo control group has also limited the confidence in the findings of this study.

Virgin coconut oil (VCO) is popularly used in the management of atopic dermatitis (AD) due to its anti-oxidant, anti-inflammatory and antibacterial properties [114]. The impact of virgin coconut oil intake on attenuation of airway/nasal inflammation has not been widely studied. One study by Kamalaldin et al. (2017) determined that the intrusion of inflammatory cells as well as the number of goblet and proliferative cells in the airway lumen was significantly lower in VCO-treated allergic asthma models [115]. The authors also inferred that VCO performed better as a rescue agent rather than a preventive one in the case of asthma. These findings, however, may not be entirely relevant for AR due to their assessment of airway inflammation only. Zainuddin et al. (2016), in their randomized-control trial, concluded that ingestion of virgin coconut oil did not improve the symptoms of

Malaysian AR patients when taken in complementary to anti-histamine (loratadine) [116]. A huge proportion of the study subjects (58.0%) reported gastrointestinal side effects throughout the 28-day period of study. This might be related to the consumption of high volume of VCO per day (30 mL) without cooking. Additionally, the exact source and composition of the VCO used in this study was not disclosed, thereby making it difficult to elucidate the findings obtained. Further studies are necessary to fully understand the effects of virgin coconut oil in the amelioration of AR symptoms.

Although not traditionally used in the management of allergic rhinitis, the efficacy of snakehead fish (*Channa striatus*) or *Haruan* supplementation as a therapeutic adjuvant for AR was researched recently. Susibalan et al. (2018) demonstrated significant improvement in nasal blockage and itchiness, alongside reduction in ocular pruritus among Malaysian allergic rhinitis patients after supplementation with oral *Channa striatus* (CS) extract [117]. This treatment was taken in complementary with anti-histamine (levocetirizine) and topical intranasal corticosteroid (fluticasone furoate) for 6 weeks. The serum IgE levels of the CS-treated group were also found to be significantly lower than that of the placebo groups' at the end of the study. This is a well-constructed randomized, double-blinded, placebo-controlled trial which could have benefitted further with a larger population size and longer study period. There were no internal side effects in the consumption of this extract as evidenced by laboratory assessments of full blood count (FBC), renal profile (RP) and liver function test (LFT). Bakar et al. (2019) further investigated changes in inflammatory markers upon oral consumption of CS extract alongside daily application of corticosteroid nasal spray (mometasone furoate) for 6 weeks [118]. They observed no significant difference in the serum eosinophil counts and IL-4 levels between treated and placebo control groups. However, within the CS-treated group itself, there were substantial improvements in the nasal symptom scores and reductions in eosinophil counts and IL-4 levels between weeks 1 and 6 of this study. This study could have included an additional control group with corticosteroid treatment alone to further validate the findings gathered. Albeit with inconclusive efficacy, the low-risk safety profiles associated with consumption of *Channa striatus* (CS) extract might be beneficial for AR patients seeking for an alternative treatment option.

Nonetheless, ingestion of any kind of natural/tropical remedies requires safe and proper dosing techniques in order to hinder harmful toxicological consequences; as depicted in one local case of accidental self-poisoning with *Datura stramonium* (*Kecubung* fruit), a highly toxic plant used traditionally for treatment of allergic rhinitis in the East Coast of Malaysia [17]. Similar cases of poisoning with seeds of this fruit had also been reported in Canada [119] and Greece [120]. The toxicity of *D. stramonium* can be attributed to the presence of tropane alkaloids and several other active bio-compounds in various concentrations throughout all parts of this plant [121]. It is therefore highly imperative that the consumption of this plant or any of its parts is discontinued until sufficient evidence is available regarding its usage in treating AR or any other disorders in general.

Besides organic medications, facial candling or *lilin resdung* is another therapeutic approach practiced primarily by the Malays for alleviation of various nasal-related conditions including flu, rhinitis and sinusitis [122]. This method involves passing of lighted herbalised candle over the patient's face for an extended period of time, as it is believed that the aroma from the herbal blend helps to promote relaxation to the patient by mainly relieving nasal pressures. Despite its claimed benefits, only mixed responses were obtained regarding the effectiveness of facial candling in countering the symptomatic effects of allergic rhinitis [123, 124].

Conclusion

The current study has comprehensively assessed and evaluated published literatures on the epidemiology, aetiology and therapy of allergic rhinitis in Malaysia. Due to limitation of data availability, the nationwide prevalence of AR in Malaysia cannot be established. Nevertheless, existing information on the percentages of recorded cases of AR among children and teenagers alone indicated distinct increments over the last few years. The reason for this might be attributed to the fact that Malaysia has been experiencing massive growths in the rates of urbanization and industrialization recently. Therefore, a modernized way of living and climatic changes owing to air pollution greatly exposes the public to putative risk factors linked with AR manifestation. Sensitization towards a myriad of biological and chemical derivatives is also of substantial importance, most of which can further aggravate the underlying allergic disorder.

Disparities in the disease distribution within different subpopulations raises the pertinent question of whether genetics, an often-overlooked player, lay the basis for allergic rhinitis susceptibility. Needless to say, scientists worldwide have managed to somewhat describe and understand noteworthy correlations between genetics and AR to a certain extent, but there is still a long way to go. Scarcity of research in this field of allergy immunogenetics in Malaysia has opened up endless possibilities for future scientific endeavours. Treatment wise, both conventional and alternative medications are meant to provide temporary relief only, although allergen-specific

immunotherapies may hold some promise in ensuring complete resolution of the allergic condition. With that being said, healthcare providers especially pharmaceutical researchers are urged to review and discover new treatment options that are personalized based on the patients' individual demographics and medical histories.

Abbreviations
AR: Allergic rhinitis; HLA: Human leukocyte antigen.

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VP and MA conceived, designed and drafted the manuscript, while FN and STS provided critical revision of the article. The authors read and approved the final manuscript.

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