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SKIN TEST REACTIVITY TO BEE HIVE PRODUCTS (HONEY BEES, HONEY, ROYAL JELLY AND POLLEN)

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Abstract

Bee hive products such as honey bees, honey, royal jelly and pollen are widely consumed as a health supplement. There has been several cases of allergic reactions to bee hive products reported worldwide. Consumption of bee hive products is common among Malaysians, but the degree of its sensitization is not known. The aim of this study is to determine the prevalence of skin test reactivity to *Apis mellifera*, domesticated locally and the bee hive products such as honey bees, honey, royal jelly and pollen among a group of volunteers. Four types of honey collected from different locations with different plant sources; one sample of imported honey from Australia, one sample of royal jelly, four different sources of bee pollen, and honey bee derivatives were used to prepare allergen extracts for skin testing. 2522 volunteers were skin tested to these allergen extracts. 271 (10.75%) of the subjects had a positive skin prick test result to at least one honey bee derivative or bee hive product allergen. Individuals with skin test positivity to honey bee are most likely to be sensitized to bee pollen followed by honey and royal jelly. Skin test reactivity to honey bee and bee hive products is prevailed to be high in Malaysia. This study has proven that bee hive products sensitization individuals are mostly to be also sensitized to honey bees. Therefore, is recommended these allergens to be included in the skin prick panel.

Keywords: Allergen; bee hive products; honey bee derivatives; prevalence

Abstrak

Produk haif lebah seperti lebah, madu, jeli raja dan debunga digunakan secara meluas sebagai makanan tambahan kesihatan. Terdapat beberapa kes reaksi alahan terhadap produk haif lebah dilaporkan di seluruh dunia. Pengambilan produk haif lebah adalah suatu kelaziman dalam kalangan rakyat Malaysia, tetapi tahap kesensitifannya tidak diketahui. Tujuan kajian ini adalah untuk menentukan prevalens kereaktifan ujian kulit terhadap *Apis mellifera*, yang diternak dalam persekitaran tempatan dan produk haif lebah seperti lebah, madu, jeli raja dan debunga dalam kalangan sekumpulan sukarelawan. Empat jenis madu yang dikumpul daripada lokasi yang berbeza dengan sumber tumbuh-tumbuhan yang berbeza; satu sampel madu yang diimport dari Australia, satu sampel jeli raja, empat sumber debunga lebah, dan derivatif lebah madu telah digunakan untuk menyediakan ekstrak alergen bagi ujian kulit. 2522 sukarelawan kulit diuji dengan ekstrak alergen tersebut. 271 (10.75%) daripada subjek menunjukkan keputusan ujian cucuk kulit yang positif terhadap sekurang-kurangnya satu alergen derivatif atau produk haif lebah. Individu yang mempunyai ujian kulit yang positif kepada lebah madu adalah paling berkemungkinan menunjukkan sensitiviti kepada debunga diikuti oleh madu dan jeli raja. Kereaktifan ujian kulit kepada lebah madu dan produk haif lebah menunjukkan prevalens yang tinggi di Malaysia. Kajian ini telah membuktikan bahawa kesensitifan individu terhadap produk haif lebah berkemungkinannya turut sensitif kepada lebah madu. Justeru, adalah disyorkan alergen-alergen ini dimasukkan ke dalam panel cucuk kulit.

Kata kunci: Alergen; produk haif lebah; derivatif lebah madu; prevalen

1.0 INTRODUCTION

Through the ages, various medicinal properties have been attributed to honey, royal jelly, bee pollen and honey bee venom. These bee hive products; i.e. honey [1-6], pollen [7-8], royal jelly [9-10], propolis [11] and honey bee venom [12-14] are widely consumed either as dietary supplements or skin applications. The

prevalence of allergy to these products among Malaysian is not known. However, there are a number of reports of allergic reactions ranging from mild symptoms to anaphylaxis from bee hive products, i.e. honey [15-17], royal jelly [18-21], bee pollen [22-23], propolis [23-5], honey bee[26-28], and honey bee venom[29-31] as described in the literatures.

Honey is a mixture of flower nectar, pollens and components from honey bees, the latter including enzyme-containing secretions from the salivary and pharyngeal glands. Recent researchers [32-34] postulated that allergic sensitization to honey is related to proteins either from pollen or honey bee origin.

Royal jelly is a secretion of the hypopharyngeal gland or worker honey bees. About 50% of its dry weight consists of proteins; other components are free amino acids, fatty acids, sugars, vitamins and some minerals. Bee pollen is flower pollen that honey bees collect for food. It is a popular health supplement that apparently boosts the immune system. Amongst the many therapeutic claims include its use in the treatment of allergies, although pollen itself is a common aeroallergen.

Ultimately, bee hive products were well documented with large number of allergens that come from the bee derivatives (saliva, body, venom), pollen (freshly foraged and comb), honey (comb and bottled), royal jelly, propolis and wax. Both positive and negative impacts, between health boosters and allergy sensitization; the consumption of bee hive products could be determined by allergy management [35].

1.1 Objectives

Consumption of honey bee by products such as honey, royal jelly and bee pollen among Malaysians is high, but the degree of sensitization is not known. The aim of this study is to determine the prevalence and pattern of skin test reactivity to these products amongst a group of volunteers.

2.0 MATERIALS AND METHODS

2.1 Source and Allergen Extracts Preparations

Four types of local honey were collected from various local apiaries. Three of these were unifloral honey (*Hevea brasiliensis*, *Cocos nucifera* and *Melalueca leucadendron*) and one sample was collected directly from the comb. One source of imported honey from Australia and royal jelly were also included in the study. Four different sources of bee pollen (collected at the entrance of the hive, comb pollen, and coconut pollen) were also collected from the local apiaries. Dried, commercial and imported pollen was also included. *Apis mellifera* honey bees were collected from an apiary in Tanjong Piai. Whole honey bee heads and nectar crops were used for allergen preparation.

Ten of honey was dissolved in 10 ml of distill water and centrifuged. The supernatant was dialyzed over two days against distill water. One gram of royal jelly was dissolved in 10 ml of distilled water. Five grams of pollen were added to 10 ml of distilled water. 30 honey bee heads and nectar crop from 30 honey bees were homogenized in 10 ml of distilled water. All the above were subjected to an overnight extraction at 4°C. The extracts were filtered and lyophilized. Extracts were reconstituted with Coca's solution before use.

2.2 Subjects

2523 volunteers from Universiti Pendidikan Sultan Idris, Perak were involved in this study. The subjects were advised not to take antihistamine two weeks prior to testing. A detailed history of allergen was obtained from each subject. Subjects were grouped into symptomatic atopic (with allergy symptoms) and familial atopic (with family members positive to allergy based on skin prick testing) allergies.

2.3 Skin Prick Test

The epicutaneous test was conducted on the volar surface of the forearm using sterile lancets. The subjects were skin tested with all the above extracts and to a range of food and inhalational allergens. Histamine (5mg/ml) and Coca's solution were used as positive and negative control respectively. Wheal size was read and recorded 15 minutes after testing. A wheal size of 3 mm or more than the negative control is regarded as positive.

2.4 Statistical Analysis

Data entry and statistical analysis were conducted using the software SPSS version 17. The risk was calculated by using Odd Ratio (OD) with Confidence Internal (CI) at 95%. The subjects' skin prick test positivity to bee hive products were grouped into honey, pollen, royal jelly and honey bees sensitizations. Other groups were food and aeroallergens.

3.0 RESULTS

Out of the 2523 subjects in the general population, 1384 (54.86%) of the subjects had a familial atopic history of allergy and 1139 (45.14%) with symptomatic atopic history. Skin prick test showed that the sensitization prevalence in the population was 37.9%. 271 (10.75%) had a positive skin test to at least one of the prepared bee hive allergens. Prevalence among the general population showed that sensitization to honey bee derivatives were the highest (8.48%), followed by bee pollen (3.17%), royal jelly (2.38%), and honey (2.10%).

This study also prevailed high prevalence of bee hive products sensitization associated to inhalant sensitization that amounted to 72.3% (196 subjects),

and to food sensitization of 61.3% (166 subjects). Among the individuals with bee hive sensitizations, 64 (23.62%) were also honey bee by products consumers. The risk for them to be also associated with food sensitization was the lowest (OR=1.75, CI 95%: 1.474 – 2.082), followed by inhalant sensitization (OR = 1.831, CI 95%: 1.600 – 2.094). They were of a higher risk to be associated to the rest of bee hive sensitizations by OR = 2.719 (CI 95%: 2.082 – 3.550).

The prevalence of 271 subjects with at least one bee hive products sensitization is as shown in Table 1. Of the subjects with positive SPT to bee hive products, 35 (12.4%) were also sensitized to at least one of the food allergens, 69 (24.5%) to any one of the inhalant allergens and 137 (48.6%) to all the three groups of allergens. It was also revealed that 10 (3.69%) were sensitized to all bee hive products. Interestingly, 57 (21.03%) of those whom were sensitized to other bee hive products, but not to the honey bees. 23 (8.49%) were sensitized to any three of bee hive products, while 60 (22.14%) to any two and 178 (65.68%) were only sensitized to one of the honey bees by products.

Table 1 Skin test reactivity prevalence to bee hive products among the 271 subjects

Allergen	No. of Subjects with Positive Skin Prick Test	Percentage
Royal jelly (N=60)	60	22.14
Honey (N=53)		19.56
H. brasiliensis	13	4.8
C. nucifera	16	5.9
M. leucadendron	16	5.9
Comb honey	32	11.8
Imported honey (Australia)	8	3.0
		29.52
Bee pollen (N=80)		
Pollen collected at the bee hive entrance	28	10.3
Comb Pollen	20	7.4
Commercial, dried pollen	48	17.7
Coconut pollen	5	1.8
		78.97
Honey bee derivatives (N=214)		
Bee head	179	66.1
Nectar crop	107	39.5

3.1 Skin Test Reactivity Pattern to 214 Subjects with Positive Skin Prick Test to Honey Bee

Individuals with skin test positivity to honey bee derivatives were most likely to be sensitized to bee pollen (23.83%), followed by honey (20.09%) and the least to royal jelly (15.42%). 129 (60.28%) individuals were sensitized to honey bee derivatives only. The positive reactivity among the honey bee towards other bee hive products is as shown in Figure 1. Positive associations were not found between positive honey bee derivatives sensitization and symptomatic atopic (OR = 1.12, 95% CI .92 to 1.35) or to familial atopic (OR = 1.02, 95% CI .87 to 1.19).

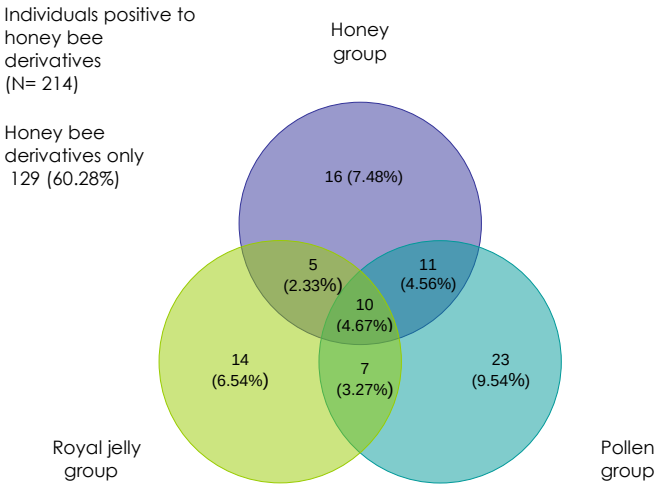

Figure1 Prevalence of subjects with honey bee sensitization associated to other bee hive products sensitizations

3.2 Skin Test Reactivity Pattern to 53 Subjects with Positive Skin Prick Test to Honey

As for those with honey sensitization, they were of the highest risk to honey bee derivatives (79.24%), bee pollen (45.28%) and royal jelly (37.74%). 4 (7.55%) were only sensitized to honey. The reactivity among the honey positivity towards honey bee and other bee hive products is as shown in Figure 2. The risk for subjects sensitized to honey to be also sensitized to honey bee derivatives was insignificant, OR=1.021 (.488 – 2.139), 95% CI). Among those who were and without the honey sensitization, the risk is insignificant with OR = 1.004 (.870 – 1.159, 95% CI) and OR = .983 (.542 - 1.785, 95% CI) respectively. Positive associations were not found between positive honey sensitization and familial atopic (OR = 1.08, 95% CI .86 to 1.35) but to symptomatic atopic (OR = 4.62, 95% CI 1.51 to 14.18).

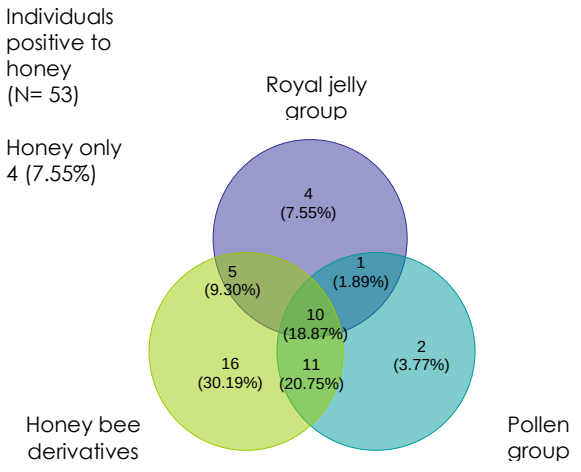

Figure 2 Prevalence of subjects with honey sensitization associated to honey bee and other bee hive products sensitizations

3.3 Skin Test Reactivity Pattern to 60 Subjects with Positive Skin Prick Test to Royal Jelly

Those with royal jelly sensitization, they have the highest risk to honey bee derivatives (58.33%), to honey (33.33%) and pollen (16.33%). A high prevalence of subjects (19, 31.67%) were sensitized to royal jelly only. The reactivities among the royal jelly positivity towards other bee hive products were as shown in Figure 3.

The calculated risk for subjects sensitized to royal jelly to also be sensitized to honey bee derivatives was at OR= .250 (.132 – .473), 95% CI). Among those who were royal jelly sensitized individuals, the risk was greater with OR = 2.682 (1.759 – 4.090, 95% CI). For those without royal jelly sensitization, they have the risk of OR = .671 (.530 - .851, 95% CI). A positive association was found between positive royal jelly skin test and non symptomatic atopic (OR = 3.13, 95% CI 1.31 to 7.46) but not to non familial atopic (OR = 1.46, 95% CI .91 to 2.34).

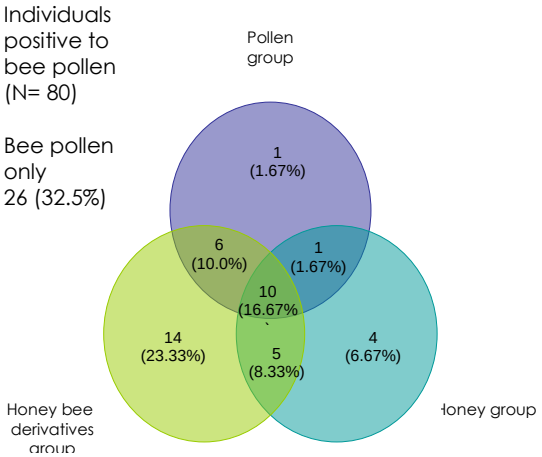

Figure 3 Prevalence of subjects with royal jelly sensitization associated to honey bee and other bee hive products sensitizations

3.4 Skin Test Reactivity Pattern to 80 Subjects with Positive Skin Prick Test to Bee Pollen

Bee pollen sensitization individuals were found to be risky to honey bee derivatives (62.50%), followed by honey (30.00%) and royal jelly (22.50%). 26 (32.50%) were found to be sensitized to only bee pollen. The reactivities among the bee pollen positivity towards honey bee and other bee hive products were as shown in Figure 4.

The calculated risk for subjects sensitized to bee pollen to also be sensitized to honey bee derivatives was at OR =.274 (.149 – .504, 95% CI). Among those who were bee pollen sensitized individuals, the risk is greater with OR = 2.253 (1.594 – 3.183, 95% CI). For those without bee pollen sensitization, they have the risk of OR =.618 (.466 - .821, 95% CI).No positive association was found between positive bee pollen sensitization and both the symptomatic atopic (OR = 1.08, 95% CI .93 to 1.25) or to familial atopic (OR = .92, 95% CI .77 to 1.10).

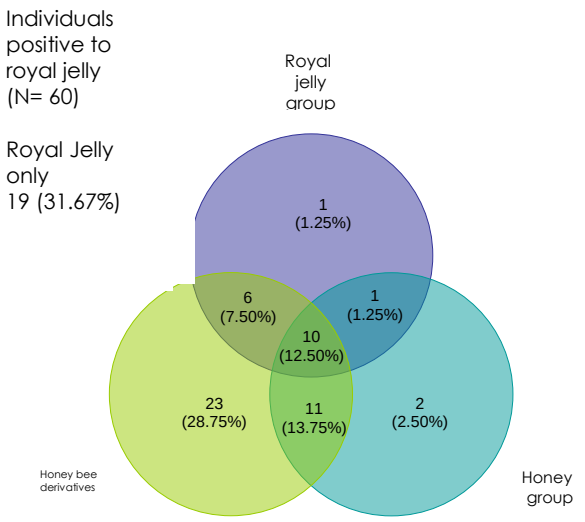

Figure 4 Prevalence of subjects with bee pollen sensitization associated to honey bee and other bee hive products sensitizations

4.0 DISCUSSION

A large percentage (54.86%) of the volunteers' skin tested to these allergen extracts had a history of allergy. 10.75% of the subjects had a positive skin prick test (SPT) to at least bee hive products allergen. In this study, bee hive product consumption among subjects with its sensitization was slightly lower (23.93%) compared to a study done by Leung *et al*. [20] which was at 31.3%. Paradoxically, the prevalence of royal jelly sensitization among the atopic subjects in their study was 7.3%, while in this study it was found that among the bee hive products sensitized subjects, the prevalence of royal jelly sensitization was 22.14%. This is three folds higher than their findings.

Hence, an assumption can be derived that the sensitization among our subjects with bee hive product sensitization is three folds more risky compared to those the atopic patients in Hong Kong general population. Therefore, caution must be taken to ensure individuals with any of the bee hive sensitization should not to be exposed or consumed these products and vice versa as they are of a more risky subject.

Although Leung *et al*. [20] found a positive association between positive royal jelly skin test and symptomatic atopic (OR = 33.73, 95% CI 4.51 to 252.11) but in this study, it showed a negative association for all the bee hive products to royal jelly. It was only honey (OR = 4.62, 95% CI 1.51 to 14.18) found to be positively associated to royal jelly sensitization.

Risks of sensitization associations between the bee hive products were described in this study. We found that royal jelly sensitization was of the highest risk to be associated to honey bee derivatives sensitization (OR = 2.682), followed by bee pollen sensitization (OR = 2.253) and the honey sensitization. Our results do not only support finding by Leung *et al*. [18-21], but also append to honey bee pollen sensitization [22-23, 34] and honey sensitizations [21, 31-32, 34].

Skin test reactivity varies among honey allergens. Comb honey (11.8%) was more "allergenic" compared to other honeys. Comb honey is an "immature" honey and at this stage, honey bee derivatives allergenic proteins such as the hyaluronic enzymes from the honey bee saliva could probably add to the allergenicity. Thus, this also explains the least skin test reactivity was with imported honey. Imported honey is prepared and comply to food standard procedures prior to exporting. One of the criteria is that the honey should comprise less than 17% moisture to prevent fermentation. This is also an indicator the honey is fully matured. Hence all allergenic proteins are digested.

Honey contains twenty to a hundred thousand pollen grains which retain their allergenic properties during the honey making process reported by Helbling *et al*. [32]. As the local bottled (rubber, Melalueca and coconut) honeys contain pollen grains, which subjects are exposed, it is not surprising that 4.8 – 5.9% of them are sensitized to them. When compared to imported honey, it contains pollen that the local population is not sensitized to. Thus, it is not surprising that it gives the least subjects (3.0%) sensitized to it.

29.5% of the bee hive products sensitized subjects also had skin test reactivity to at least one type of bee pollen. The preparation of commercial bee pollen starts with collecting the pollen trapped at the entrance of the bee hive, followed by the drying process. The commercial bee pollen used in this study is not a local product, but it is widely consumed. The entrance bee pollen allergen was prepared from fresh bee pollen collected at the bee hive entrance. Comb pollen is different from entrance pollen. Once the forager honey bee enters the hive, worker honey bees then 'process' the pollen by mixing it with honey bee saliva and plant nectar. The process could enhance allergenicity to it.

Ironically, this study showed more individuals were skin test positive to the commercial bee pollen. The entrance pollen was second, followed by comb pollen and the coconut pollen. Although the comb pollen is with the most contact with the honey bee derivatives allergenic proteins, but the "fanning" process of converting plant nectar into honey may bring the same effect on comb pollen by denaturing the allergenic proteins. Therefore, the comb pollen has less sensitized subjects compared to the entrance honey. The highest prevalence of sensitization to the commercial bee pollen could be explained that it has been observed as the most widely consumed. Subsequently, the subjects are well exposed to it and due to this, it gives rise to the higher prevalence.

Bee products are promoted as a health tonic to boost the immune system and as treatment for allergies. Interestingly, we found that there was a

positive association between the skin test reactivity to house dust mites and bee hive products (OR = 1.831, CI 95%: 1.60 – 2.09). This was also reported by Thien *et al*. [19] and they suggested that cross-reactivity between house dust mite and the honey bee component might account for the high prevalence of skin test reactivity to royal jelly in their population. They assumed this could probably due to the presence of honey bee component in royal jelly. In our study population symptomatic atopic individuals were more likely to be sensitized to these bee hive products. Other investigators to list a few, Mansfield and Goldstein [23], Helbling *et al*. [31] and Florida-Lopez *et al*. [15] have expressed their concern with regards to this issue.

From the pattern of skin test reactivity to bee hive products, it can be assumed that allergic sensitization to honey is related to proteins from either honey bee derivatives or the nectar or pollen those in contact with the honey bee. Studies by Dutau [31] suggested differently, that if serums IgE from individuals with honey bees sensitization are able to bind to a large number of honey proteins and the prevalence of honey allergies could be alleviated in those allergenic to hymenopterans or among the beekeepers. At present we are conducting further studies to identify and characterize all the possible allergenic proteins that are involved in the bee hive products sensitization. Avoidance is always the recommendation to allergy management. Therefore, removing the allergenic proteins is the option to lighten the problem, but it would be tough as bee hive products are often used as the ingredients and hidden in food, food supplements and energy products.

5.0 CONCLUSION

Skin test reactivity to bee hive products is prevailed to be high in Malaysia. As this study has proven that bee hive products sensitized individuals are mostly to be also sensitized to honey bees. Therefore, it is highly recommended that honey bee by product allergens to be included in the skin prick panel.

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