

CHAPTER 4

Discussion

This study was conducted in subjects with persistent AR. The subjects were randomized equally to receive a second-generation antihistamine, the generic cetirizine (Zertine®), combined with oral capsules of *A. ascalonicum* L. or the identical placebo capsules for 4 weeks. The efficacy and safety of this study were evaluated by using the subjective and objective assessments. AR symptoms that comprised with nasal symptoms and ocular symptoms were the main outcomes for this study. The nasal symptoms described as, “total nasal symptom score (TNSS)” included itchy nose, nasal obstruction, sneezing, and rhinorrhea. The total ocular symptom score (TOSS) included itchy eyes, watery eyes, and eye redness.

The results showed that VAS, TNSS, and TOSS were improved in both groups without statistical difference between groups. This finding indicated the efficacy of the generic cetirizine as the standard treatment for AR when the medicine was used continuously for at-least 2 weeks. Rhinorrhea seemed to be the first symptom that reduced immediately after 1 week of treatment and have the great impact on the subjects’ TNSS and VAS. The efficacy of the oral shallot supplement was presented in the results that only the subjects in the shallot group showed significant improvement of sneezing, itchy nose and eyes since the second week of treatment.

Theoretically, mast cells are the key factors in the allergic and inflammatory reaction after the patients expose to allergens. They rapidly and specifically produce various mediators and cytokines such as histamines, tumor necrosis factor (TNF), proteases, leukotrienes, prostaglandins, interleukin-4 (IL-4), and IL-5. These mediators from mast cells result in increasing of vascular permeability, mucus production, activation of nerve cells, and enhancement of effector-cells (neutrophils, eosinophils)

recruitments [60-62]. All of these processes lead to the AR symptoms such as itchy nose, nasal obstruction, sneezing, rhinorrhea, and ocular symptoms.

Mast cell stabilizer such as disodium cromoglicate (DSCG), ketotifen, nedocromil sodium, and olopatadine are used in AR and asthmatic patients. However, because of the mast cell heterogeneity and the application which required several administrations per day result in the need to investigate the newly mast cell stabilizer from natural sources. There are many mast cells stabilizing agent from natural sources such as coumarins, terpenoids, and flavonoids. Flavonoids can be subdivided into several classes including flavones, flavonols, flavonones, isoflavones, flavovols-3-ols, and anthocyanidins. Quercetin is the derivative from flavonoid in flavonols class [63]. Quercetin has many pharmacological effects including anti-allergic activity through antioxidant activities [64, 65], inhibition of histamine and other chemical mediators, as well as stabilization of mast cells [63, 66, 67].

The exact mechanism of how shallot help easing the allergic symptoms is not fully understood. Similar to other plants in Lily family, there are many components in shallot, for example, alliin (S-allyl cysteine sulfoxide), dipropyl disulfide, diallyl disulfide, and flavonoids [30, 31]. However, there are many polyphenolic derivatives such as quercetin, quercetin 4'-glucoside, quercetin 7,4'-diglucoside, quercetin 3,4'-diglucoside, quercetin aglycone, quercetin mono-D-glucose, isorhamnetin 3,4'-diglucoside, and isorhamnetin 4'-glucoside in the shallot [32, 34-36, 68, 69]. Nevertheless, the effect of quercetin as mast cell stabilizer prevents mast cells from degranulate the histamine. After level of histamine is decreased, nasal mucosal inflammation is reduced, thereby improvement of AR symptoms [70].

There are many kinds of vegetables and fruits that have been tested and positive for anti-allergic activities, for instance, sweet potatoes, lotus, mints, and onions. Onion is one of the plants in Lily family associated with shallot that has been shown the anti-allergic activity [71, 72]. Oral intake of 360 mg tomato extract that contains flavonoid components for 8 weeks have been shown to reduce sneezing, rhinorrhea and nasal obstruction in AR patients [73]. In another clinical study, 200 mg of enzymatically modified isoquercitrin (EMIQ) was given orally to patients with Japanese cedar pollinosis

for 8 weeks as compared with placebo [65]. Interestingly, the results from that study were similar to the results of this preliminary study. In EMIQ study, TOSS and itchy eyes of patients in the EMIQ group were significantly lower than the placebo group through the antiallergic and antioxidant effects [65, 69, 74]. Correspondingly, severity of itchy eyes was reduced remarkably in the patients received oral shallot supplement for 4 weeks.

From the study results, itchy eyes was significantly reduced in only in the subjects who received oral shallot supplement combined with generic cetirizine for 2 and 4 weeks. In spite of statistically insignificant between groups, we still believed that the use of oral shallot supplement may benefit the treatment of allergic rhinoconjunctivitis (Hay fever) or any AR patients whose main disturbing symptoms are sneezing and itchiness.

Nasal obstruction was the only symptom that slightly improved after the treatment for 3 weeks by cetirizine with or without oral shallot supplement. Likewise, NAR was not changed at all after the treatment in both groups. This finding meant the pathophysiology that causes nasal obstruction in AR does not rely solely on the histaminergic pathway but from different mediators. Leukotrienes, thromboxanes, and prostaglandin D₂ (PGD₂) which causes nasal mucosa swelling and venous engorgement and leading to nasal obstruction. These mediators cause nasal obstruction via cellular infiltration and accumulation such as eosinophils, neutrophils, basophils, and lymphocytes. Especially, eosinophils are the mainly cell types that characterize the late phase reaction. For this reason, mostly result in nasal obstruction which is the main symptom of AR patients in late reaction [75]. Additionally, the results from other studies imply that not only histamine, leukotrienes, and PGD₂ but also other mediators. Bradykinin associates with the nasal obstruction via B₂ receptor and eosinophilia in the human nasal airway [76-78]. Therefore, antihistamine medication could not strongly improve nasal obstruction in the AR patients. In turn, we could imply that oral shallot supplement had no decongestant effect.

Conversely, intranasal corticosteroids are usually effective for all of AR and allergic conjunctivitis symptoms, including the late phase symptom like nasal congestion [79]. Intranasal corticosteroids decrease the influx of inflammatory cells and release the inflammatory mediators in the nasal mucosa via alteration in protein synthesis and transcription factors after binding to the steroid receptors complex to DNA [19, 80].

According to the “Allergic Rhinitis with its Impact on Asthma” or ARIA guideline 2008 and the ARIA 2016 revision, the intranasal corticosteroids are recommended for using alone or in combination with oral antihistamines in AR patients [4, 19, 81]. We suggest that the further study may focus on the efficacy of the use of oral shallot supplement in combination with intranasal corticosteroids because the greater clinical outcome is possible. The role of shallot in AR is probably due to its function as mast cell stabilizer.

For nasal cytology, it was performed by scraping of the mucosal epithelium from left and right inferior turbinates. This technique is cheap, simple, and safe [82]. After treatment, the inflammatory cells such as neutrophils, eosinophils, and basophils were slightly decreased from baseline without statistically significant in both groups. After the end of treatment, these inflammatory cells were not significantly different between groups. Lymphocytes and macrophages were not found before and after treatment. This finding was similar to the previous study that the inflammatory cell were not seen in 11% of AR patients before the treatment [83]. Moreover, Morakot *et al* found that the number of each inflammatory cell are increased and decreased from baseline after 4 weeks of mometasone furoate and fluticasone furoate treatment in AR patients [84].

Although the efficacy of oral shallot supplement for AR patients was not robust in this study, there were adequate data to confirm the effectiveness and safety of the 3-gram intake of oral shallot, equivalent to 1½ bulbs, from Thai traditional remedy [18]. The similar amounts of shallot were used in general as ingredients of many famous Thai cuisine such as Tom-Yam soup and sauces, or dressings to add flavor to simple dishes.

From chemical assessment of shallot capsules for the quality standard control of Thai FDA guidelines for herbal products, the amount of quercetin found in the capsule sample was 0.0019 mg/ml (6.29 µmol/L). Previous study demonstrated that there were anti-inflammatory and antiallergic effects when the concentration of quercetin ranged between 0.2 µmol/L to 1 mmol/L [85]. Therefore, it is reasonable to eat shallots for health promotion, anti-inflammation, and anti-allergic reaction. Moreover, inulin was found 33.22% in the dry shallot [86]. Inulin is the prebiotic found in many potential food plants in Thailand such as garlic and onion. It has many nutritional and health benefits such as dietary complex, caloric fiber, reduction in risk of gastrointestinal disease, and stimulation of immune system [87]. So, the further study about inulin in the shallot seems

interesting. However, since this was the first study about shallot in AR patients, the limitation of this study was the insufficient data for shallot dosing and interval of administration. Therefore, the further study about the pharmacokinetic of shallot is important.

During the study, one of various confounding factors that could affect the patients' AR symptoms was the allergen exposure and environmental factors. Subjects who participated in this study during February to April were highly affected by smog, air pollution known as burning season in the Northern of Thailand. The exposure to air pollution of particulate matter (PM) in the air led to direct irritation of nasal epithelium and worsen nasal and ocular symptoms. PM incurred from intense traffic, burning, industrial system, and chemical reaction of PM in the atmosphere. Small PM or fine PM (PM_{2.5}) can pass through airway included alveoli and terminal bronchioles. For this reason, PM_{2.5} can generate many airway symptom and inflammation of pulmonary via imbalance of the ratios of T-helper 1 Cells to T-helper 2 Cells (Th1/Th2) and increasing oxidative stress [88]. Various study demonstrated that PM_{2.5} exposure associated with risk and severity of AR [89-91]. In the same way, some subjects who were allergic to house dust mites could not avoid dust mites exposure during their home or workplace renovation.

Patients' compliance is another important factors to achieve good clinical outcome for AR. In this study, 15 subjects were excluded from final analysis due to the less-than 85% of treatment compliance, resulting in a small size of subjects. A further clinical trial with larger sample size and longer duration of shallot use should be continued to verify the efficacy and safety. Moreover, many literatures have demonstrated that AR patients usually take AR medication as needed rather than the continuous use [92].

The myth of Thai herbal knowledge mentioned that eating too much of shallots (more than 3 bulbs) per day may cause side effect such as decrease strength of hair roots [18]. However, this study found that these side effects did not differ from the placebo when shallots were eaten 1 and half bulbs per day. Adverse events (AEs) were similar in both groups, such as dizziness, fatigue, headache, rash, dry mouth and throat, nausea, and dyspepsia. Furthermore, somnolence appeared to be caused by the generic cetirizine rather than the oral shallot supplement. Previous study showed that the mechanism of

somnolence or sedative effects of antihistamines arise from blocking of depolarizing responses at the human cortical neurons via H₁-receptor [93]. Generally, sedative effects of the second-generation antihistamines are less than first-generation antihistamines [79]. However, sedative effects of antihistamine rely on their occupancy of H₁-receptor (holding between antihistamine and H₁-receptor). The occupancy of H₁-receptor on non-sedative is less than 20% but the occupancy of H₁-receptor of cetirizine vary between 10-30% [94, 95]. Therefore, some patients who received the cetirizine were found the somnolence. Differ from others second-generation antihistamines such as levocetirizine, fexofenadine that very low occupancy of H₁-receptor (0.1%) [81, 96-98] so there were not present the somnolence or sedative effect after taking that medicine. Alternatively, the mainly data of occupancy of H₁-receptor incurred from healthy volunteers. Hence, it should consider that the reaction of AR affected to capillary permeability in both peripheral and blood-brain barrier. In addition, nasal and ocular symptoms in AR patients affected to sleep that may be influence to somnolence. However, no serious adverse event (AE) was found in this study.



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