Bisdemethoxycurcumin attenuates OVA-induced food allergy by inhibiting the MAPK and NF-κB signaling pathways

YANJIE WANG, PING ZHANG, JINGYU ZHANG and TIE HONG

Department of Pharmacology, School of Pharmaceutical Sciences, Jilin University, Jilin, Changchun 130021, P.R. China

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Abstract. Bisdemethoxycurcumin (BDMC) is an important ingredient derived from turmeric in addition to curcumin. It has been reported that BDMC can be used to treat mast cell-mediated allergic diseases. In the present study, a food allergy (FA) murine model sensitized by intraperitoneal injection followed by oral challenge with ovalbumin (OVA) was established. BDMC was orally administered at 100 and 200 mg/kg for 11 days in the challenge phase to treat OVA-induced FA mice. FA symptoms such as diarrhea score, anaphylactic symptom score and rectal temperature were recorded. Intestinal tissue was also observed by hematoxylin and eosin staining. In addition, other allergic indicators were also analyzed by ELISA and western blot analysis. The present study demonstrated that BDMC could suppress the decreases in rectal temperature, diarrhea and anaphylactic symptoms in FA mice. BDMC could also ameliorate the inflammation of intestinal tissues in FA mice. BDMC not only decreased the production of OVA-specific immunoglobulin (OVA-sIg)E, IgG1, histamine, mouse mast cell protease-1, diamine oxidase, cytokines (IL-4, IL-5 and IL-13) but increased cytokines interferon-γ production. The protein expression results showed that the levels of Gata-3 were decreased but T-bet levels were increased. Furthermore, compared with the OVA group, phosphorylated (p)-p38, p-JNK, p-ERK and p-NF-κBp65 levels were decreased and p-IκBα level was increased. In conclusion, the results showed that BDMC possessed a protective effect on FA. Furthermore, BDMC was able to regulate the T-helper cells (Th)1/Th2 immune balance and inhibit the activation of MAPK and NF-κB pathways in FA mice.

Introduction

Food allergy (FA) is a rapidly growing public health problem worldwide (1-4). In recent years, the incidence of FA has been increasing (5). FA can cause a series of allergic disease complications such as hives, asthma and diarrrhea, which can put human health at risk (6,7). Food allergens are usually some proteins that can cause hypersensitive responses. The main allergic responses are attributed to only a limited variety of proteins that are considered the main allergens of foods (8). Among the limited proteins, ovalbumin (OVA), which accounts for 54% of the protein in egg white, is a major cause of allergic reactions in humans, especially in children (9,10).

A number of studies have demonstrated that most FAs are immunoglobulin E (IgE)-mediated type 1 hypersensitivity reactions, which depend on antigen-specific differentiation of helper T cell (Th) 2 cells in the sensitization phase and degranulation and cytokine production of mast cells and basophils in the effect phase (11-13). MAPK signaling serves an important role in the cell differentiation, cell activation, cell proliferation, degranulation and cell migration of various immune cells (14). MAPK signaling is involved in mast cell regulating the production of cytokines in response to specific extracellular stimuli and then initiates biological reactions (15). Among the kinases, p38 participates in the production of proinflammatory cytokines by regulating the expression of NF-κB (16).

Bisdemethoxycurcumin (BDMC) is an ingredient derived from turmeric in addition to curcumin, which has been shown to have effects on food allergies and allergic rhinitis (17-19). BDMC is a relatively stable component in vivo and is more readily absorbed into the cell nucleus than curcumin (20,21). BDMC possesses anticancer, antioxidant and antibacterial properties (22-24). Additionally, BDMC has been shown to have inhibitory effects on mice with OVA-induced allergic rhinitis in our previous study (25). In the present study, the effects of BDMC were evaluated in a murine model of FA.

Materials and methods

Mice. In total, 36 female BALB/c mice weighing 18-22 g were purchased from Liaoning Changsheng Biotechnology Co., Ltd. Mice were housed in an air-conditioned room (temperature 25±2°C, relative humidity 55±5%) with a 12 h light/dark cycle and ad libitum food and water. All animal experiments were approved by the Institutional Animal
Care and Use Committee of Jilin University (approval no. 20200050).

**Induction of FA mice.** To induce FA, 36 mice were divided into the Control group, OVA group, BDMC low-dose group (100 mg/kg; MilliporeSigma) and BDMC high-dose group (200 mg/kg; n=9/group). As previously described (17,18) and depicted in Fig. 1, the mice in all groups except the Control group were intraperitoneally (i.p.) injected with 50 µg OVA (MilliporeSigma) in 50 µl aluminum hydroxide (2 mg; Beijing Solarbio Science & Technology Co., Ltd.) dissolved in saline on days 0, 7 and 14 and the Control group was administered i.p. saline injections of the same amount. From day 28-38, all groups except the Control group were challenged intragastrically (i.g.) with 50 mg OVA, which was dissolved in 250 µl phosphate buffered saline (PBS) every other day for a total of six times and the Control group was given the same solvent. Mice were starved for 3-4 h before each intragastric challenge to ensure that the OVA antigen could quickly pass through the stomach without being destroyed by gastric acid.

**Drug treatment.** Following our previous research (25), drug treatment groups were orally treated with BDMC (100 and 200 mg/kg; MilliporeSigma) in 1% carboxy methyl cellulose (CMC) every day from day 28-38. The Control group and OVA group were given only 1% CMC. The mice were anesthetized with an intraperitoneal injection of 50 mg/kg pentobarbital sodium and sacrificed by cervical dislocation 1 h after the sixth challenge.

**Evaluation of allergic symptoms.** Diarrhea scores were estimated as: 0, normal stools; 1, a little wet, unshaped stools; 2, a small amount of wet and unshaped stools with moderate perianal staining of the coat; and 3, severe and watery stools with severe perianal staining of the coat (17). Anaphylactic symptoms were evaluated according to a scoring system from previous reports (26). Symptom scores were rated as follows: 0, no symptoms; 1, scratching around the nose and head; 2, swelling around the eyes and mouth; 3, wheezing, difficult respiration, cyanosis around the mouth and tail; 4, no activity after stimulation or tremors and convulsions; and 5, death. Rectal temperature was measured by a thermometer within 60 min and the rectal temperature change of the mice in each group was also calculated.

**Histological analysis.** The jejunal tissues were fixed in 10% neutral formalin for 4 h at room temperature (RT) and embedded in paraffin. The slides (4-µm thick) were stained with hematoxylin and eosin (HE) for 30 sec at RT. The numbers of inflammatory infiltrates in individual samples were measured in a blinded manner. The number of inflammatory cells in the five fields with the most infiltrates for each mouse was calculated in a blinded manner. Images were obtained using a light microscope (Leica Microsystems, Inc.; x400 magnification) for detection of inflammatory cell infiltration.

**Enzyme-linked immunosorbent assay.** The levels of OVA-specific immunoglobulin (OVA-sIg)E, IgG1, histamine, mouse mast cell protease-1 (mMCP-1), diamine oxidase (DAO) and cytokines (IL-4, IL-5, and IL-13) and interferon-γ (IFN-γ) in serum were analyzed by commercially available ELISA kits (Shanghai Enzyme-linked Biotechnology Co., Ltd.), according to the manufacturer's instructions. OVA-sIgE (cat. no. ml063583), OVA-sIgG1 (cat. no. ml037615), histamine (cat. no. ml001877), mMCP-1 (cat. no. ml037840), DAO (cat. no. ml002199-C), IL-4 (cat. no. ml063156-J), IL-5 (cat. no. ml063157) and IL-13 (cat. no. ml063157).

**Western blot analysis.** Total proteins were resolved from the mouse intestinal jejunal tissue with RIPA buffer (Genstar Biosolutions Co., Ltd.) supplemented with protease inhibitors, including PMSF (Genstar Biosolutions Co., Ltd.). The protein concentrations were measured using the BCA Protein Assay kit (Beyotime Institute of Biotechnology). Protein (~20-40 µg) was electrophoresed on 10% SDS-PAGE and then electroproated with a PVDF membrane. The separated proteins were transferred to PVDF membranes (Beyotime Institute of Biotechnology), which then were put into TBS-T (Tris-buffered saline, 0.1% TWEEN 20) solution containing 5% skimmed milk and shaken for 2 h at room temperature to avoid non-specific binding. Then, the membranes were incubated with primary antibodies (1:1,000) at 4°C overnight and then incubated with specific HRP-conjugated secondary antibodies (1:4,000) for 1 h at room temperature. Finally, the signals were visualized using an enhanced chemiluminescence reagent. The densitometry was calculated using ImageJ (version no. 20150116; National Institutes of Health).

**Statistical analysis.** Data analyses were performed using the SPSS 20.0 statistical software package (IBM Corp.) and GraphPad Prism software (version 5.0; GraphPad Software, Inc.). The experimental data were expressed as the mean ± standard deviation (SD) or individual values. One-way analysis of variance was used to evaluate significant differences between multiple groups, followed by Dunnett’s post hoc test using GraphPad Prism software (version 5.0; GraphPad Software, Inc.). For diarrhea and symptom scores, Kruskall-Wallis followed by Dunn's multiple comparison test was used. P<0.05 was considered to indicate a statistically significant difference.

**Results**

**Effect of BDMC on FA symptoms.** The results showed that while OVA group mice exhibited severe profuse diarrhea compared with the Control group, the BDMC low-dose group, BDMC high-dose group mice showed a lower diarrhea score compared with the OVA group (Fig. 2A). Similarly, OVA group mice exhibited severe anaphylaxis reactions compared with the Control group. In contrast, the anaphylaxis symptom scores of the mice in the BDMC low-dose group and the BDMC high-dose group were reduced (Fig. 2B). The results showed that the rectal
temperature of mice in the OVA group decreased by 3.01˚C within 60 min compared with the Control group. Furthermore, decreased rectal temperature was significantly suppressed by BDMC in a dose-dependent manner (Fig. 2C). The results also indicated that the rectal temperature changes in the OVA group was significantly decreased, while treatment with BDMC attenuated the decrease in rectal temperature in mice (Fig. 2D).

**Effect of BDMC on the histology of jejunum tissue and DAO levels in serum.** For improved understanding of the effect of BDMC on the intestinal tissue in FA mice, HE staining of the jejunum tissue of each group of mice was performed. As shown in Fig. 3A, the OVA group showed shorter and blunt villi and obvious inflammatory cell infiltration and intestinal villus edema compared with the Control group. However, intestinal villus edema was relieved, inflammatory cell infiltration was significantly improved and intestinal tissue morphology was relatively complete when treated with different doses of BDMC. Similarly, the level of DAO in serum of OVA group mice was significantly higher than the Control group. Compared with the OVA group, the level of DAO in serum in both the BDMC low-dose and high-dose groups exhibited a significant decrease (Fig. 3B).
Effect of BDMC on the levels of OVA-sIgE, OVA-sIgG1, histamine and mMCP-1 in serum. Compared with the Control group, mice in the OVA group produced higher levels of OVA-sIgE and OVA-sIgG1. BDMC treatment significantly reduced the levels of serum OVA-sIgE (Fig. 4A) and OVA-sIgG1 (Fig. 4B). Additionally, compared with those in the Control group, histamine (Fig. 4C) and mMCP-1 (Fig. 4D) levels in serum in the OVA group were significantly increased and their levels were decreased significantly after the administration of BDMC.
Effect of BDMC on the levels of cytokines in serum. In the OVA group, Th2 cytokines (IL-4, IL-5 and IL-13) were increased and oral treatment with different doses of BDMC significantly reduced its levels (Fig. 5A, B, C). T-helper cells (Th1) cytokine, such as IFN-γ, was decreased in the OVA group and its level was increased after BDMC treatment (Fig. 5D). In particular, the BDMC high-dose group (200 mg/kg) suppressed the production of IL-4, IL-5 and IL-13 and increased IFN-γ production.

In addition, the key transcription factors T-bet for the Th1 immune response and Gata-3 for the Th2 immune response were checked at the protein level and the results were similar to the results of Th1/Th2 cytokines. The protein level of Gata-3 in the OVA group was upregulated, while the protein level of T-bet was significantly downregulated compared with the Control group. However, after BDMC treatment, the protein level of Gata-3 was downregulated, while the protein level of T-bet was upregulated in a dose-dependent manner (Fig. 5E and F).

Effect of BDMC on the activation of MAPK and NF-κB pathway. The expression levels of the related proteins of MAPK pathway such as p-p38, p38, p-JNK, JNK, p-ERK and ERK were evaluated by western blot analysis (Fig. 6A and B). The results demonstrated that the levels of p-p38, p-JNK and p-ERK in the OVA group were markedly upregulated compared with those in the Control group. When treated with different doses of BDMC, their expression levels were dose-dependently downregulated. Additionally, the expression levels of the NF-κB pathway-related proteins p-NF-κBp65 and p-IκBα were evaluated (Fig. 6C and D). Similarly, the results showed that the protein expression level of p-NF-κBp65 in the OVA group was upregulated and the protein expression level of p-IκBα was downregulated compared with the Control group. Particularly, BDMC reversed their expression levels.

Discussion

Our previous study found that BDMC possesses inhibitory effects on mice with OVA-induced allergic rhinitis and other allergic diseases (25), but its anti-food allergies have not been studied. FA is a type of immune adverse reaction caused by food, which includes a range of disorders such as IgE-mediated anaphylaxis, a decrease in rectal temperature and gastrointestinal adverse reactions (27,28). FA symptoms
have previously been reported to be the result of a complex immune response involving the systemic, gastrointestinal and mucosal immune systems (29,30). Anaphylactic symptoms and rectal temperature are associated with systemic immune responses and diarrhetic symptoms are related to the gastrointestinal immune system (30). In the present study, the diarrhea scores and symptom scores were significantly reduced following BDMC treatment. The administration of different doses of BDMC also significantly reduced the rectal temperature of mice with FA. Therefore, the results indicated that BDMC has an important effect on systemic immunity and the gastrointestinal immunity.

According to previous reports, mice with FA exhibit intestinal tissue inflammatory cell infiltration and severe edema of intestinal tissue (31,32). In line with these studies, the HE staining results of jejunum tissue in the present study confirmed that BDMC can reduce inflammatory cell infiltration and intestinal villus edema to maintain the integrity of the intestinal tissue structure. In particular, DAO is one of the most important enzymes that is regarded as an indicator of changes in intestinal permeability in FA mice (33). OVA-induced FA mice have been reported to have elevated expression levels of DAO (34). Consistent with these studies, the results of the present study showed that BDMC could reduce the level of serum DAO of FA mice to maintain the integrity of the intestinal mucosa.

FA is mainly a hypersensitivity response mediated by IgE that binds primarily to the high-affinity IgE receptor (FceRI) and cross-links with mast cells allergen. Allergen-stimulated mast cells cause their degranulation; then, histamine and mMCP-1 are released, causing allergic symptoms (32,35). Other immunoglobulins (such as IgG1) also serve a key role in the basic regulatory mechanism of allergic inflammation (36). In addition, histamine is a key mediator that can cause allergic symptoms in FA mice and mMCP-1 is one of the mast cell proteases found in mucosal mast cells (37-39). Previous studies have shown that OVA-sIgE, OVA-sIgG1, histamine and mMCP-1 levels are significantly increased in mice with FA (40-42). Consistent with these studies, the results of the present study demonstrated that BDMC could decrease the levels of OVA-sIgE, OVA-sIgG1, histamine and mMCP-1 in serum to exert effects against food allergies.

Following ingestion of food allergens, T cells from intestinal-associated lymphoid tissues, spleen and many other immune tissues are activated to differentiate into other Th cell lineages (43,44). Among them, immune cells including CD4+ T cells secret cytokines (IL-4, IL-5, IL-13 and IFN-γ) to maintain the immune balance (45,46). In particular, it is reported that serum IL-4, IL-5 and IL-13 levels are higher and IFN-γ levels are lower in FA mice (17). Based on the above studies, of the present study indicated that BDMC not only significantly increased the levels of IL-4, IL-5 and IL-13 but also significantly decreased the level of IFN-γ.

Regarding protein expression, T-bet, the key nuclear transcription factor of the Th1-type immune response and Gata-3, the key nuclear transcription factor of the Th2-type immune...
response, have been reported (26). The results of the present study also demonstrated that BDMC significantly increased the expression of T-bet and decreased the expression level of Gata-3 in FA mice. Therefore, the data demonstrated that BDMC improves the Th1/Th2 response balance to attenuates FA symptoms.

Additionally, the activation of basophils and mast cells includes a complex network of signaling pathways and molecules, including a type of tyrosine kinases and MAPKs (47). p38 MAPK is important for human allergic reactions (48). Furthermore, NF-κB activation typically requires the phosphorylation of IκB by the IκB kinase complex, which results in IκB degradation and subsequent translocation of NF-κB to the nucleus, which serves an important role of innate immune defense (49,50). It has also been reported that BDMC is able to inhibit cytokine secretion and the activation of NF-κB and the breakdown of IκB and improve human mast cell inflammation by inhibiting MAPK and NF-κB pathways (51). Based on the above studies, the present study demonstrated that BDMC could inhibit the activation of the MAPK signaling pathway and nuclear translocation of NF-κB in FA mice. The significance of this result is crucial for the treatment of FA.

In conclusion, the present study shows that BDMC has inhibitory effects on mice with OVA-induced food allergy. The effectiveness of the mechanism underlying BDMC may involve regulating the Th1/Th2 balance and inhibiting the activation of the MAPK and NF-κB pathway in FA mice. This discovery may have important implications for the treatment and further research of FA.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Authors’ contributions
YW and TH conceived and designed the study. YW, PZ and JZ collected and analyzed the data. YW and TH confirm the authenticity of all the raw data and wrote the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The experimental protocols were approved by the Institutional Animal Care and Use Committee of Jilin University (approval no. 20200050).

Patient consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

References
1. Prescott S and Allen KJ: Food allergy: Riding the second wave of the allergy epidemic. Pediatr Allergy Immunol 22: 155-160, 2011.
2. Johnston LK, Chien KB and Bryce PF: The immunology of food allergy. J Immunol 192: 2529-2534, 2014.
3. Sicherer SH: Epidemiology of food allergy. J Allergy Clin Immunol 127: 594-602, 2011.
4. Sicherer SH and Sampson HA: Food allergy: Recent advances in pathophysiology and treatment. Annu Rev Med 60: 261-277, 2009.
5. Venter C and Arshad SH: Epidemiology of food allergy. Pediatr Clin North Am 58: 327-349, 2011.
6. Krogulska A, Polakowska E, Wasowska-Królikowska K, Małachowska B, Młynarski W and Borowiec M: Decreased FOXP3 mRNA expression in children with atopic asthma and IgE-mediated food allergy. Ann Allergy Asthma Immunol 115: 415-421, 2015.
7. Kucuk ZY, Strait R, Khodoun MV, Mahler A, Hogan S and Finkelman FD: Induction and suppression of allergic diarrhea and systemic anaphylaxis in a murine model of food allergy. J Allergy Clin Immunol 129: 1343-1348, 2012.
8. Gendel SM: Bioinformatics and Food Allergens. J AOAC Int 87: 1417-1422, 2004.
9. Bernhisel-Broadbent J, Dintzis HM, Dintzis RZ and Sampson HA: Allergenicity and antigenicity of chicken egg ovalbumin (Gal d III) compared with ovalbumin (Gal d I) in children with egg allergy and in mice. J Allergy Clin Immunol 93: 1047-1059, 1994.
10. Van Asperen P, Kemp AS and Mellis CM: Skin test reactivity and clinical allergen sensitivity in infancy. J Allergy Clin Immunol 73: 381-386, 1984.
11. Sampson HA: Food allergy. Part 1: Immunopathogenesis and clinical disorders. J Allergy Clin Immunol 103 (5 Pt 1): 717-728, 1999.
12. Yu W, Freeland DMH and Nadeau KC: Food allergy: Immune mechanisms, diagnosis and immunotherapy. Nat Immunol 16: 751-765, 2015.
13. Kumar S, Verma AK, Das M and Dwivedi PD: Molecular mechanisms of IgE-mediated food allergy. Int Immunopharmacol 13: 432-439, 2012.
14. Duan W and Wong WS: Targeting mitogen-activated protein kinases for asthma. Curr Drug Targets 7: 691-698, 2006.
15. Li L, Zhang XH, Liu GR, Liu C and Dong YM: Isoquercitrin suppresses the expression of histamine and pro-inflammatory cytokines by inhibiting the activation of MAP Kinases and NF-κB in human KU812 cells. Chin J Nat Med 14: 407-412, 2016.
16. Zhou Y, Yang Q, Xu H, Zhang J, Deng H, Gao H, Yang J, Zhao D and Liu F: MiRNA-221-3p Enhances the secretion of interleukin-4 in mast cells through the phosphatase and tensin Homolog/p38/Nuclear Factor-kappaB pathway. PLoS One 11: e0148821, 2016.
17. Shin HS, See HJ, Jung SY, Choi DW, Kwon DA, Bae MJ, Sung KS and Shon DH: Turmeric (Curcuma longa) attenuates food allergy symptoms by regulating type 1/2 helper T cells (Th1/Th2) balance in a mouse model of food allergy. J Ethnopharmacol 175: 21-29, 2015.
18. Kinney SR, Carlson L, Ser-Dolansky J, Thompson C, Shah S, Gambrah A, Xing W, Schneider SS and Mathias CB: Curcumin ingestion inhibits mastocytosis and suppresses intestinal anaphylaxis in a murine model of food allergy. PLoS One 10: e0132467, 2015.
19. Zhang N, Li H, Jia J and He M: Anti-inflammatory effect of curcumin on mast cell-mediated allergic responses in ovalbumin-induced allergic rhinitis mouse. Cell Immunol 298: 88-95, 2015.
20. Gordon ON, Luis PB, Ashley RE, Osheroff N and Schneider C: Oxidative transformation of demethoxy- and bisdemethoxycurcumin: Products, mechanism of formation, and poisoning of human topoisomerase IIα. JACS Chem Res Toxicol 28: 989-996, 2015.
21. Ramezani M, Hatamipour M and Sahebkar A: Promising Anti-tumor properties of Bisdemethoxycurcumin: A naturally occurring curcumin analogue. J Cell Physiol 233: 880-887, 2018.
22. Xu JH, Yang HP, Zhou XD, Wang HJ, Gong L and Tang CL: Role of Wnt inhibitory factor-1 in inhibition of bisdemethoxycurcumin mediated epithelial-to-mesenchymal transition in highly metastatic lung cancer 95D cells. Chin Med J (Engl) 128: 1376-1383, 2015.

23. Li YB, Gao JL, Zhong ZF, Hoi PM, Lee SM and Wang YT: Bisdemethoxycurcumin suppresses MCF-7 cells proliferation by inducing ROS accumulation and modulating senescence-related pathways. Pharmacol Rep 65: 700-709, 2013.

24. Haukvik T, Bruzell E, Kristensen S and Tønnesen HH: A screening of curcumin derivatives for antibacterial phototoxic effects Studies on curcumin and curcuminoids. XLIHI. Pharmazie 66: 69-74, 2011.

25. Fu M, Fu S, Ni S, Wang D and Hong T: Inhibitory effects of bisdemethoxycurcumin on mast cell-mediated allergic diseases. Int Immunopharmacol 65: 182-189, 2018.

26. Lee D, Kim HS, Shin E, Do SG, Lee CK, Kim YM, Lee MB, Min KY, Koo J, Kim SJ, et al: Polysaccharide isolated from Aloe vera gel suppresses ovalbumin-induced food allergy through inhibition of Th2 immunity in mice. Biomed Pharmacother 101: 201-210, 2018.

27. Sicherer SH and Sampson HA: Food allergy: Epidemiology, pathogenesis, diagnosis, and treatment. J Allergy Clin Immunol 113: 291-307, 2013.

28. Berin MC: Pathogenesis of IgE-mediated food allergy. Clin Exp Allergy 45: 1483-1496, 2015.

29. Sicherer SH and Sampson HA: Food allergy: Epidemiology, pathogenesis, diagnosis, and treatment. J Allergy Clin Immunol 125 (Suppl 2): S116-S125, 2010.

30. Kweon MN, Yamamoto M, Kajiki M, Takahashi I and Kiyono H: Histamine and histamine intolerance. Expert Rev Clin Immunol 11: 1321-1331, 2015.

31. Yamaki K and Yoshino S: Remission of food allergy by the Janus kinase inhibitor ruxolitinib in mice. Int Immunopharmacol 18: 175-185, 2009.

32. Bischoff S and Crowe SE: Gastrointestinal food allergy: Systemically derived large intestinal CD4(+) Th2 cells play a central role in STAT6-mediated allergic diarrhoea. J Clin Invest 106: 199-206, 2000.

33. Conley M, Pasternak A, Costello MC, Egan AM, Turner MS, et al: Polysaccharide isolated from Aloe vera gel suppresses ovalbumin-induced food allergy through inhibition of Th2 immunity in mice. Biomed Pharmacother 101: 201-210, 2018.

34. Wang M, Takeda K, Shiraishi Y, Okamoto M, Dakahama A, Joetham A and Gelfand EW: Peanut-induced intestinal allergy is mediated through a mast cell-IgE-FcepsilonRI-IL-13 pathway. J Allergy Clin Immunol 126: 306-316, 316.e1-12, 2010.

35. Galli SJ, Tsai M and Piliponsky AM: The development of allergic inflammation. Nature 454: 445-454, 2008.

36. Ciprandi G, Marseglia GL, Castagnoli R, Valsecchi C, Tagliacarne C, Caimmi S and Licari A: From IgE to clinical trials of allergic rhinitis. Expert Rev Clin Immunol 11: 1321-1331, 2015.

37. Wang M, Takeda K, Shiraishi Y, Okamoto M, Dakahama A, Joetham A and Gelfand EW: Peanut-induced intestinal allergy is mediated through a mast cell-IgE-FcepsilonRI-IL-13 pathway. J Allergy Clin Immunol 126: 306-316, 316.e1-12, 2010.

38. Hua X and He SH: Roles of histamine and its receptors in allergic and inflammatory bowel diseases. World J Gastroenterol 11: 2851-2857, 2005.

39. Manti L and Novak N: Histamine and histamine intolerance. Am J Clin Nutr 85: 1185-1196, 2007.

40. Yamamoto T, Fujikawa K, Yoshida M, Kageyama-Yahara N, Kuramoto H, Shibahara N and Kadowaki M: Therapeutic effect of kakkonto in a mouse model of food allergy with gastrointestinal symptoms. Int Arch Allergy Immunol 148: 175-185, 2009.

41. Brandt EB, Stratt RT, Hershko D, Wang Q, Muntele EE, Scribner TA, Zimmemann N, Finkelman FD and Rothenberg ME: Mast cells are required for experimental oral allergen-induced diarrhea. J Clin Invest 112: 1666-1677, 2003.

42. Matsui T, Yamashita H, Mori M, Tanaka H and Inagaki N: Epipikajutsuto protects against food allergy induced by ovalbumin in a murine model. Int Arch Allergy Immunol 173: 71-83, 2017.

43. Wang C, Collins M and Kuchroo VK: Effector T cell differentiation: Are master regulators of effector T cells still the masters? Curr Opin Immunol 37: 6-10, 2015.

44. Cook PC, Jones LH, Jenkins SJ, Wynn TA, Allen JE and MacDonald AS: Alternately activated dendritic cells regulate CD4+ T-cell polarization in vitro and in vivo. Proc Natl Acad Sci USA 109: 9977-9982, 2012.

45. Yamane H and Paul WE: Cytokines of the γc family control CD4+ T cell differentiation and function. Nat Immunol 13: 1037-1044, 2012.

46. Manise M, Holtappels G, Van Crombruggen K, Schleif F, Bachert C and Louis R: Sputum IgE and cytokines in asthma: Relationship with sputum cellular profile. PLoS One 8: e58388, 2013.

47. Gilfillan AM and Tkaczyk C: Integrated signalling pathways for mast-cell activation. Nat Rev Immunol 6: 218-230, 2006.

48. Qi M and Elion EA: MAP kinase pathways. J Cell Sci 118(Pt 16): 3569-3572, 2005.

49. Azzolina A, Bongiovanni A and Lampiasi N: Substance P induces TNF alpha and IL-6 production through NF kappa B in peritoneal mast cells. Biochim Biophys Acta 1643: 75-83, 2003.

50. Schuliga M: NF-kappaB signaling in chronic inflammatory airway disease. Biomolecules 5: 1266-1283, 2015.

51. Kong R, Kang OH, Seo YS, Zhou T, Kim SA, Shin DW and Kwon DY: MAPKs and NF-kB pathway inhibitory effect of bisdemethoxycurcumin on phorbol-12-myristate-13-acetate and A23187-induced inflammation in human mast cells. Mol Med Rep 17: 630-635, 2018.

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