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

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Received September 26, 2021; Accepted February 1, 2022

DOI: 10.3892/etm.2022.11328

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.

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Key words: bisdemethoxycurcumin, food allergy, T-helper cells 1/2, MAPK, NF-κB

Introduction

Food allergy (FA) is an 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 diarrhea, 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) 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 jejunum 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 jejunum 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 electroporated 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). Anti-p38 (cat. no. bs-33423M), anti-phosphorylated (p)-p38 (cat. no. bs-0636R), anti-JNK (cat. no. bs-0636R), anti-p-JNK (cat. no. bs-4163R), anti-ERK (cat. no. bsm-33337M), anti-p-ERK (cat. no. bs-3016R), anti-IκBα (cat. no. bs-1287R), anti-p-IκBα (cat. no. bs-5514R), anti-NF-κB p65 (cat. no. bs-23216R), anti-p-NF-κB p65 (cat. no. bs-0982R) primary antibodies were purchased from BIOSS; anti-β-actin (cat. no. AA128) primary antibody was purchased from Beyotime Institute of Biotechnology. Goat anti-mouse IgG (cat. no. NC-AP124P) and goat anti-rabbit IgG (cat. no. NC-AP1332P) secondary antibodies were purchased from Changchun Changsheng Life Sciences.

Statistical analysis. Data analyses were performed using the SPSS 20.0 statistical software package (IBM Corp.) and GraphPad Prism 6.2 software (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 evaluated 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

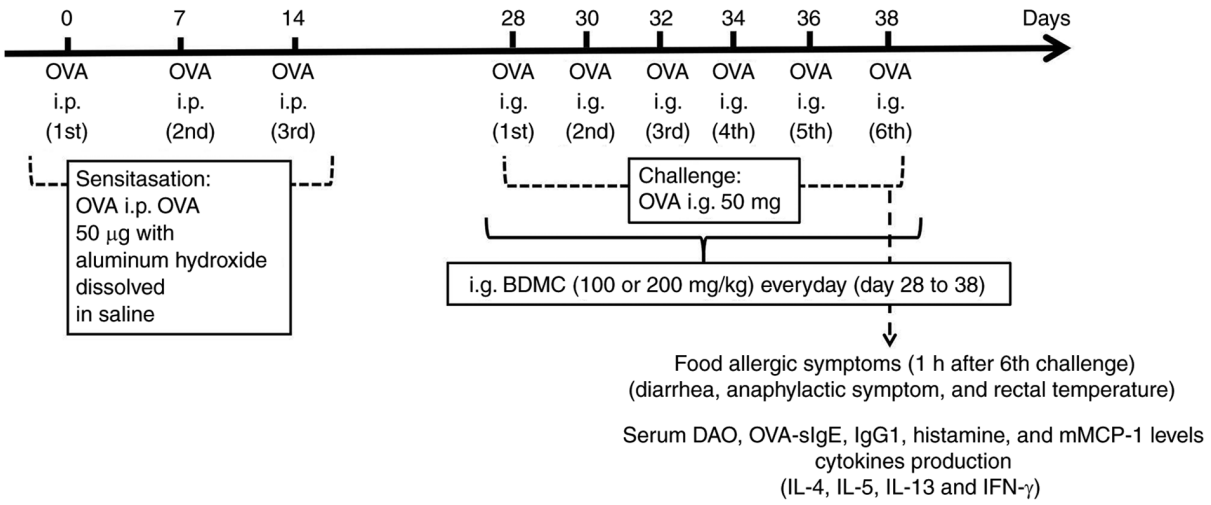

Figure 1. Experimental schedule of OVA-induced FA in a mouse model. To induce FA, mice were divided into Control group (n=9), OVA group (n=9), BDMC low-dose group (100 mg/kg; n=9) and BDMC high-dose group (200 mg/kg; n=9). Mice in all groups except the Control group were intraperitoneally (i.p.) immunized with 50 μg OVA in 50 μl aluminium hydroxide (2 mg) dissolved in saline on the 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 in 250 μl PBS every other day for a total of six times. Drug treatment groups was orally treated with BDMC (100 and 200 mg/kg) in 1% CMC every day from day 28 to 38. OVA, ovalbumin; FA, food allergy; BDMC, bisdemethoxycurcumin.

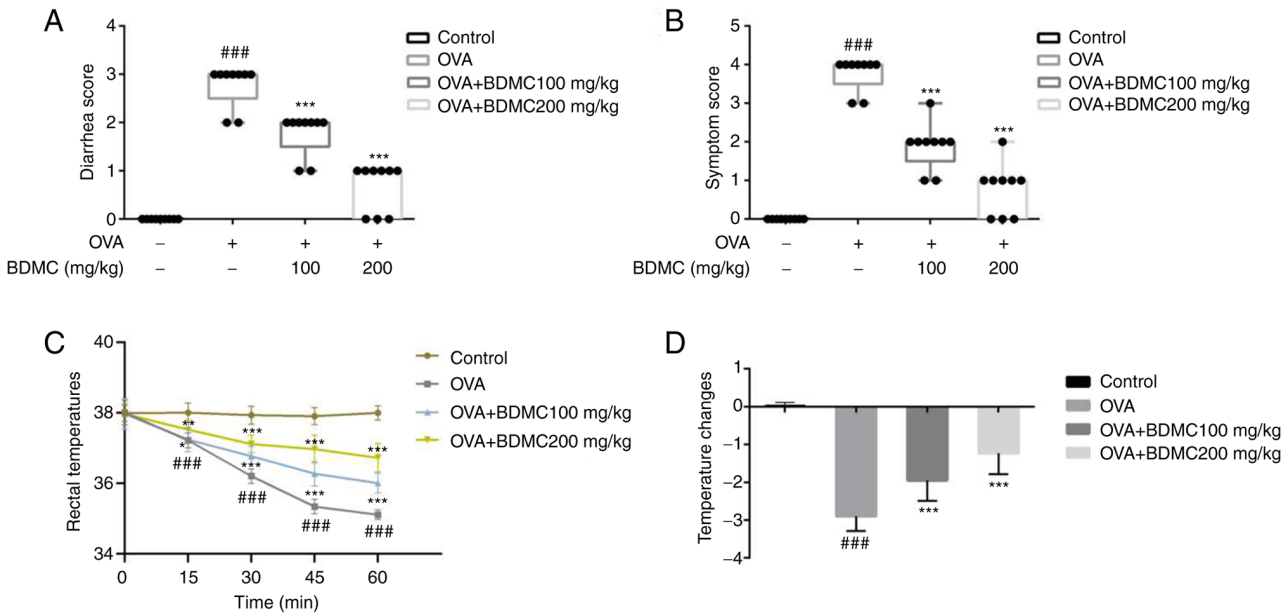

Figure 2. Effects of BDMC on OVA-induced FA symptoms. OVA-induced FA symptoms were evaluated (decreased rectal temperature, anaphylactic response and diarrhea) for 1 h after the last challenge with OVA. (A) Diarrhea score of different groups. (B) Symptom sores of different groups. (C) Rectal temperature time curve. (D) Rectal temperature changes. The data are presented as the mean ± standard deviation. Data are representative of 3 independent experiments. n=9/group. $^{###}$P<0.001 vs. Control group; *P<0.05, **P<0.01, ***P<0.001 vs. OVA group. BDMC, bisdemethoxycurcumin; OVA, ovalbumin; FA, food allergy.

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).

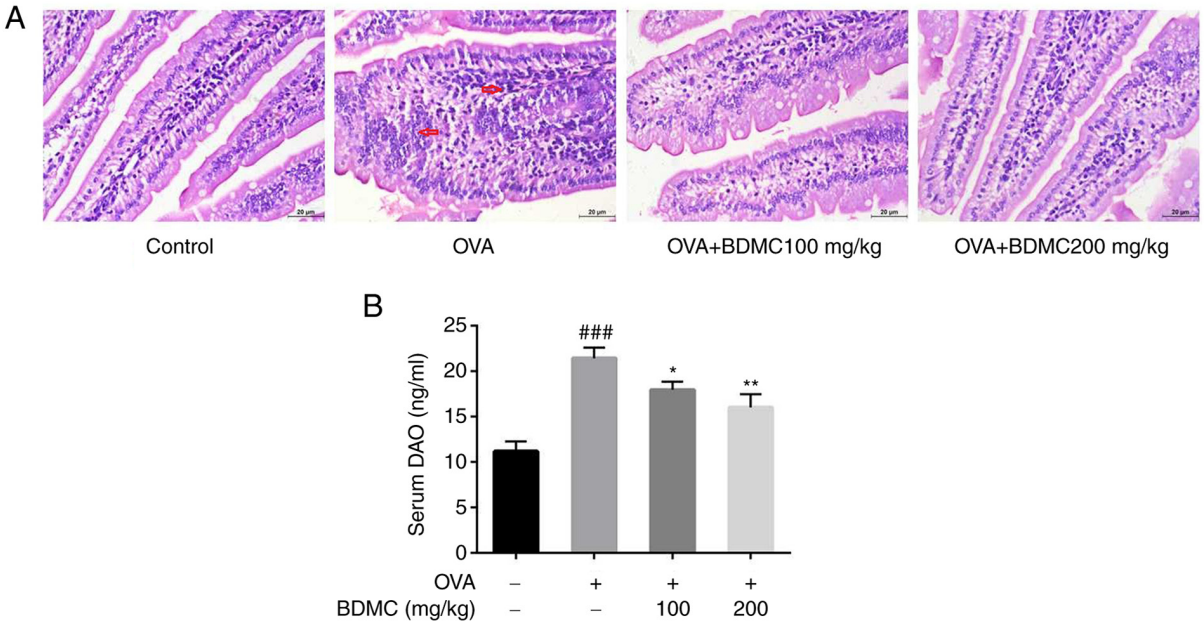

Figure 3. Effect of BDMC on histology of the jejunum tissue and DAO levels in serum. (A) Observation of inflammatory cell infiltration and intestinal tissue structure in jejunum tissue by hematoxylin and eosin staining (magnification, x400). (B) Level of serum DAO of mice in all groups. The data are presented as the mean ± SD. ###P<0.001 vs. Control group; *P<0.05, **P<0.01 vs. OVA group. BDMC, bisdemethoxycurcumin; DAO, diamine oxidase; OVA, ovalbumin.

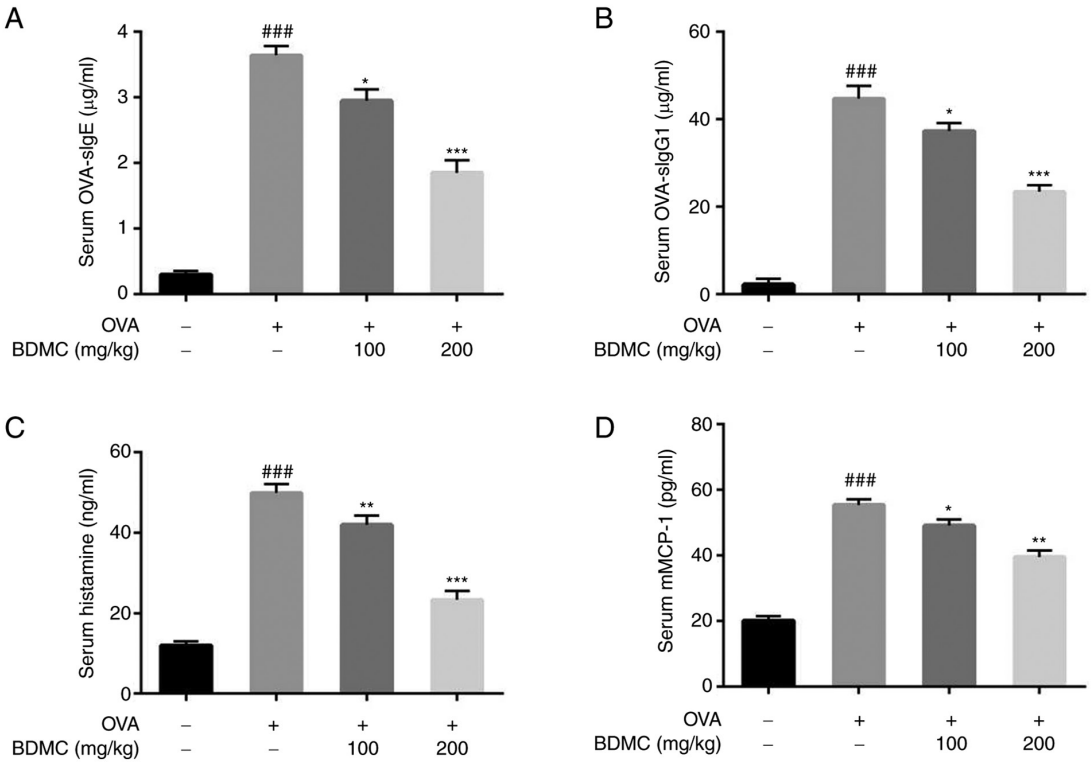

Figure 4. Effect of BDMC on OVA-sIgE, OVA-sIgG1, histamine, mMCP-1 levels in serum. Level of serum (A) OVA-sIgE, (B) OVA-sIgG1, (C) histamine and (D) mMCP-1 of mice in all groups. The data are presented as the mean ± standard deviation. Data are representative of 3 independent experiments. n=9/group. ###P<0.001 vs. Control group; *P<0.05, **P<0.01, ***P<0.001 vs. OVA group. BDMC, bisdemethoxycurcumin; OVA-sIg, OVA-specific immunoglobulin; mMCP-1, mouse mast cell protease-1; OVA, ovalbumin.

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.

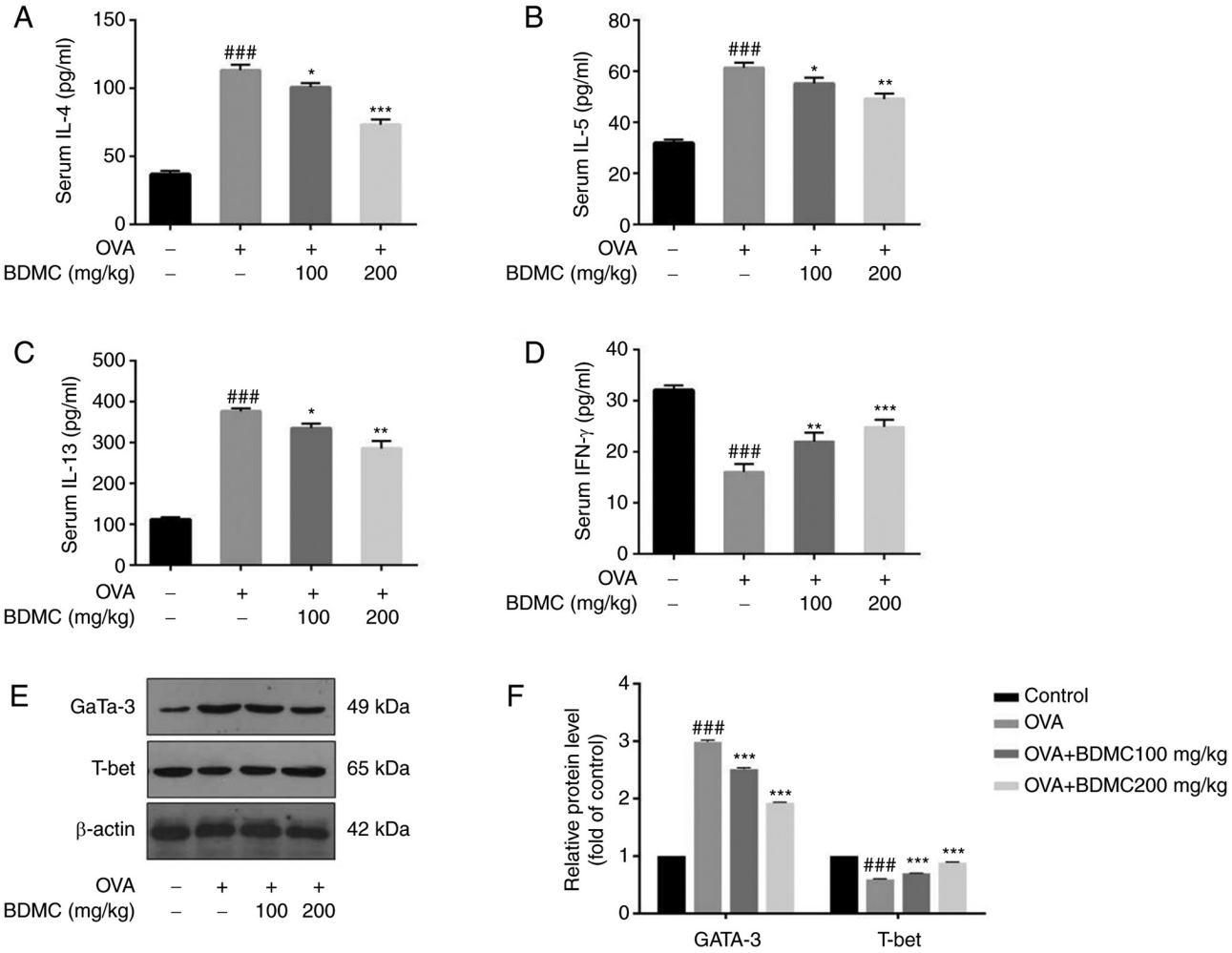

Figure 5. Effect of BDMC on the levels of Th1 cytokines and Th2 cytokines in serum. Cytokines from serum were analyzed by ELISA. (A) IL-4, (B) IL-5 and (C) IL-13 were measured as Th2 cytokines. (D) Th1 cytokine IFN-γ was measured. (E and F) The protein levels of Gata-3 and T-bet of different groups were analyzed by western blot analysis. Data are presented as the mean ± standard deviation. Data are representative of 3 independent experiments. n=9/group. $^{###}$P<0.001 vs. Control group; *P<0.05, **P<0.01, ***P<0.001 vs. OVA group. BDMC, bisdemethoxycurcumin; Th, T-helper cells; OVA, ovalbumin.

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 (Th)1 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

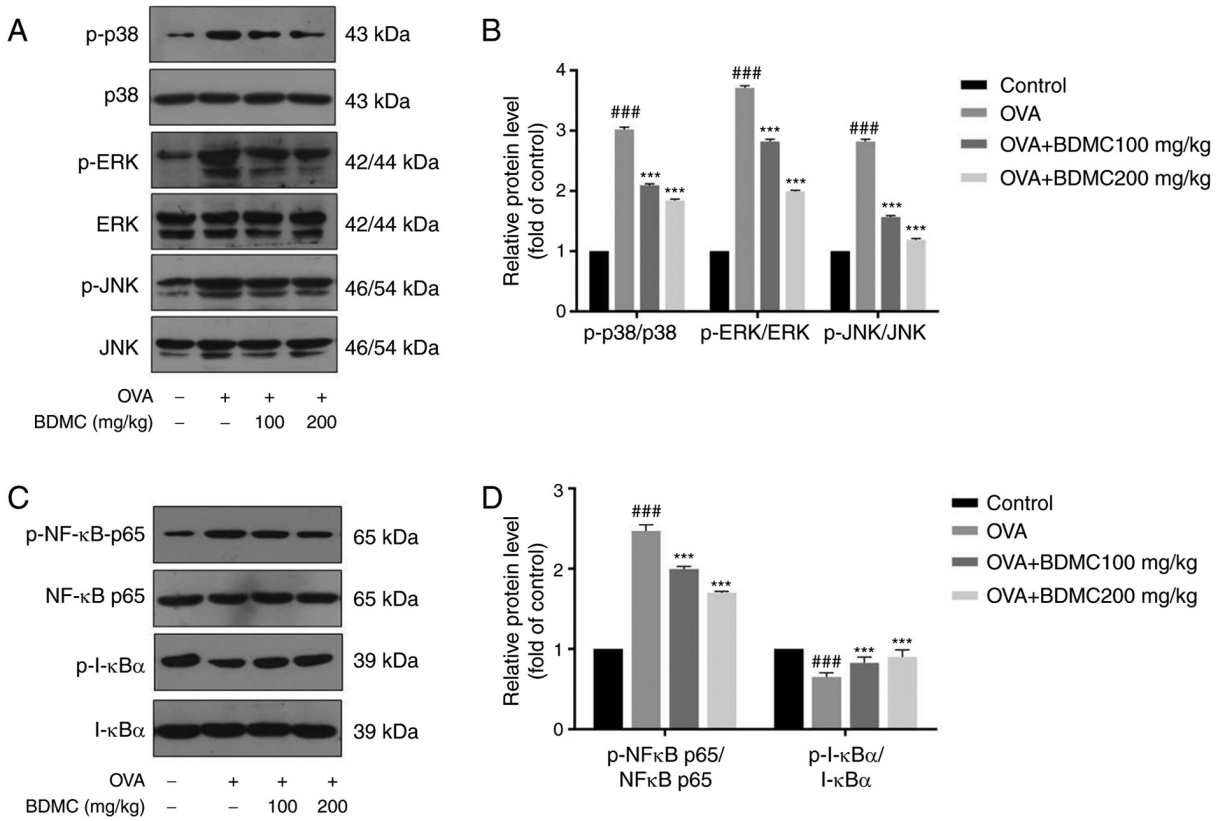

Figure 6. Effects of BDMC on the activation of MAPK and NF-κB pathway. (A and B) The expression levels of MAPK pathway related proteins p-p38, p38, p-JNK, JNK, p-ERK and ERK by western blot analysis. (C and D) The expression levels of NF-κB pathway related proteins p-NF-κBp65, NF-κBp65, IκBα and p-IκBα. The density of each band was quantified by ImageJ Software. The data are presented as the mean ± standard deviation. Data are representative of 3 independent experiments. $^{###}$P<0.001 vs. Control group; ***P<0.001 vs. OVA group. BDMC, bisdemethoxycurcumin; p-, phosphorylated; OVA, ovalbumin.

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 (FcεRI) 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.

Acknowledgements

Not applicable.

Funding

No funding was received.

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.

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