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Original article

Fisetin and telmisartan each alone or in low-dose combination alleviate OVA-induced food allergy in mice

Reem Elkholy[a], Mohamed Balaha[b,a,*], Noha El-Anwar[c], Samah Kandeel[d], Sabiha Hedya[a], Mohamed-Nabih Abd-El Rahman[a,e]

[a] Pharmacology Department, Faculty of Medicine, Tanta University, Tanta, Egypt
[b] Department of Clinical Pharmacy, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Saudi Arabia
[c] Pathology Department, Faculty of Medicine, Tanta University, Tanta, Egypt
[d] Histology Department, Faculty of Medicine, Tanta University, Tanta, Egypt
[e] Pharmacology Department, Faculty of Medicine, Bisha University, Saudi Arabia

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ABSTRACT

Background: Food allergy (FA) is a worldwide health problem, affecting nearly 10% of all populations, with no prophylactic options or regulatory treatment available until now. Fisetin, a biologically active flavonoid, and telmisartan, the highly selective competitive AT1 receptor antagonist, recently exhibited potent anti-inflammatory and immunomodulatory activities. In the present study, we have evaluated the possible anti-inflammatory and immunomodulatory activities of fisetin and telmisartan each alone or in low-dose combination in a mouse model of FA.

Methods: For induction of FA, eight-week-old BALB/c mice, sensitized by two *ip* injection of 50 μg ovalbumin (OVA) and 1 mg alum at day 0 and 7. Then, each mouse challenged with 10 mg OVA at days 14, 16, 18, and 21. On the 28th day, the fifth challenge carried out by oral administration of 50 mg OVA. Either fisetin (1 or 3 mg/kg/d), telmisartan (1 or 3 mg/kg/d) or a combination of fisetin 1 mg/kg/d and telmisartan 1 mg/kg/d received orally from the 13th day till 28th day. In challenge days, the treatments received one-hour before the challenge.

Results: Our data showed that fisetin and telmisartan each alone or in low-dose combination attenuated the anaphylactic manifestation, decreased blood eosinophilic count, serum OVA-specific IgE, and IL-4 levels, the intestinal total and degranulated mast cells count, and CD4^{+} immunohistochemical expression. Furthermore, they enhanced the serum IFN-γ level and abrogated the intestinal histopathological changes induced by OVA in mice.

Conclusion: Either fisetin, telmisartan or their low-dose combination could be promising in the management of FA.

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Introduction

Food allergy (FA) is a worldwide health problem affecting nearly 10% of all populations, with an increasing prevalence [1]. Its development is due to the breakdown of barriers, with sensitization of the susceptible individuals. This sensitization results into the differentiation of CD4^{+} naïve cells into T-helper 2 (Th2) cells that encourages the imbalance of Th1/Th2 cytokine secretions, with a predominance of Th2 cytokine secretion, such as interleukin (IL) -4, and suppression of Th1 cytokine secretion, such as interferon (IFN)-γ [2,3]. Hence, it enhances the B-cell proliferation and differentiation into immunoglobulin (Ig)-E secreting plasma cells, with increasing of the intestinal IgE level that attached to mast cells and basophils, which mediate local immunologic reactions, through the promotion of their degranulation, and release of their mediators, such as histamine on re-exposure to the allergen [3,4].

Furthermore, there is growing evidence that angiotensin-II plays a crucial role in the development of hypersensitivity reactions and promotion of inflammatory cascades *via* stimulation of AT1 receptor [5–8]. Moreover, angiotensin II exerts pro-inflammatory effects on leukocytes, especially T lymphocytes, leading to its activation, with subsequent secretions of the inflammatory cytokine, thus activating innate and adaptive

* Corresponding author.
E-mail address: Mohamed.Balaha@Med.Tanta.Edu.Eg (M. Balaha).

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immune mechanisms, with the recruitment of inflammatory cells, and thereby amplifying the inflammatory responses [7,9–11]. Additionally, it acts in an autocrine fashion, as it activates T lymphocytes through AT1 receptor stimulation. Then the activated T lymphocytes secrete angiotensin II locally, thus augmenting its activities [6,12]. Besides, it promotes dendritic cells' (DCs) migration and antigen-presenting ability, *via* stimulation of its AT1 receptors [13,14]. Hence, the blockade of the AT1 receptor could hinder the immunomodulatory and inflammatory activities of angiotensin II, and ameliorate its hypersensitivity induced reactions [5,7,11], with consequent interruption of FA development and progression.

However, still, there are no specific prophylactic options available for FA, except for strict avoidance, which is too hard to do. In addition, there is no regulatory treatment for FA approved until now. Moreover, the present medications have many side effects, do not stop the progression of hypersensitivity reactions, and not so effective [15,16]. Therefore, we are in great need to search for a new agent, preferably of herbal origin, to control the food-induced allergic reactions, likewise, the modulation of a new pathogenesis of FA that could suppress the hypersensitivity reactions and prevent its progression.

Fisetin (3, 7, 3′, 4′-tetrahydroxyflavone) is one of the dietary biologically active polyphenolic compounds that widely distributed in fruits and vegetables such as strawberry, apple, persimmon, grape, onion and cucumber [17,18]. It proved to have pleiotropic effects, including anti-inflammatory, antioxidant, antiproliferative, neuroprotective, and antidepressant activities [19–22]. In addition, it has an immunosuppressive effect on ovalbumin (OVA) induced allergic airway inflammation through its immunomodulatory, anti-inflammatory activities, and suppression of nuclear factor kappa beta cascade [23,24].

Furthermore, telmisartan is a highly selective direct, competitive, non-peptide AT1 receptor antagonist that used for the treatment of many cardiovascular disorders such as hypertension and heart failure [25]. It exhibits a powerful direct and indirect, through the AT1 receptor blockade, anti-inflammatory, antioxidant and immunomodulatory capabilities in different experimental models [26–28]. Moreover, it is an agonist for the nuclear peroxisome proliferator-activated receptor gamma (PAPR-γ), which proved to suppress eosinophilic airway inflammation through its anti-inflammatory activities, as a result of DCs inhibition [29,30]. Additionally, it recently reported protecting against OVA-induced airway remodeling in rats, through its bronchodilator, antioxidant, and anti-inflammatory abilities [8].

Consequently, in the present study, we have evaluated the possible anti-inflammatory and immunomodulatory activities of fisetin and telmisartan each alone or in low-dose combination on a mouse model of FA, regarding for, FA manifestations, serum OVA-specific IgE, cytokines and intestinal histopathological changes, mast cell degranulation, and immunohistochemical $CD4^+$ expression.

Materials and methods

Drugs and chemicals

Ovalbumin (OVA, Grade V) and fisetin (Sigma Aldrich, St. Louis, MO., USA), telmisartan (Boehringer Ingelheim Pharm. Co., El Mohandseen, Giza, Egypt), dexamethasone (Memphis Pharm. & Chem. Ind., Al Amirya, Alex., Egypt), phosphate buffered saline (PBS), carboxymethyl cellulose (CMC), aluminum hydroxide (alum), formalin buffered saline, Giemsa stain and ethylene-diamine-tetra-acetic acid (EDTA) buffer (Al-Gomhoria Pharm. Co., Tanta, Egypt), anti-$CD4^+$ polyclonal antibody (Biorbyt, CA, USA), ketamine (Sigma, Nasr City, Cairo, Egypt), and xylazine (Adwia, Obour City, Cairo, Egypt).

Animals

In the present study, eight-week-old BALB/c mice, weighing 20–25 g, used (Tanta University Animal House). The animals kept at room temperature, 12-h light/dark cycle, with free access to standard laboratory food and water *ad-libitum*. All the experimental manipulations followed the guidelines of the care and use of experimental animal in the Faculty, with the approval of its Animal Experiment Committee (Approval code 20,141,222).

Induction of FA

FA induced by the modification of the method described by Matsui et al. Briefly, each mouse actively sensitized by two intraperitoneal (*ip*) injection of 50 μg OVA and 1 mg alum in 0.2 ml PBS at day 0 and 7. Then, each mouse challenged every other day by oral administration of 10 mg OVA in 0.25 ml PBS, for four times starting from the 14th day of the experiment. One week after the 4th challenge, the 5th challenge carried on by oral administration of 50 mg OVA in 0.25 ml PBS [31].

Experimental design and sample collections

Mice randomly divided into 9 groups of 8 mice each. Group I (CON), normal mice sensitized and challenged with PBS. Group II (OVA), ovalbumin-induced FA-group. Group III (CMC), FA-group that received 0.5% CMC daily. Group IV (DX), FA-group, which received 0.5 mg/kg/d dexamethasone (standard-reference-group) [32]. Group V (FL), FA-group that received 1 mg/kg/d fisetin. Group VI (FH), FA-group, which received 3 mg/kg/d fisetin [23]. Group VII (TL), FA-group, which received 1 mg/kg/d telmisartan. Group VIII (TH), FA-group, which received 3 mg/kg/d telmisartan [33]. Group IX (FT), FA-group, which received 1 mg/kg/d fisetin and 1 mg/kg/d telmisartan. The treatment's doses chose according to dose-response pilot studies (not shown here). All treatments suspended in 0.5% CMC, prepared fresh daily and received orally from the 13th day till the 28th day of the experiment. On the challenge days, the treatments received 1 h before the challenge. One h after the last challenge, the mice anesthetized with *ip* injection of 80 mg/kg ketamine and 5 mg/kg xylazine, then blood collected; as after oral administration fisetin Tmax is 13.3 ± 1.7 min, t1/2 is 67.9 ± 24.5 and nearly disappeared from serum by 120 minutes, then serum harvested and stored at −80 °C for further assessment [34]. Afterward, the mice euthanized by cervical dislocation, dissected, and the proximal jejunum collected, washed with PBS, and immediately fixed in 10% formalin buffered saline for assessment of intestinal histopathological changes, mast cell degranulation, and immunohistochemical $CD4^+$ expression.

Assessment of FA manifestations

The FA manifestations evaluated by the assessment of the rectal temperature change and the diarrheal score. The rectal temperatures measured just before and 1 h after the last challenge, using a digital thermometer, Beurer GmbH, Germany [35]. However, the diarrheal score evaluated immediately after the last challenge, where each mouse placed in an individual cage and monitored for 1 h. Then, diarrhea scored arbitrarily as follow, 0, no fecal changes, 1, soft but well-formed faces, 2, soft and non-formed faces, 3, one episode of liquid diarrhea, 4, at least two episodes of liquid diarrhea and 5, score 4 plus only clear liquid in the colon at the sacrifice [36].

Assessment of blood eosinophilic count

One h after the last challenge, a blood drop from mouse-tail spread over a slide, fixed with methanol, stained with Giemsa stain, and examined on ×400 magnification for standard morphological criteria, and expressed as a percentage of 300 white blood cells counted [37].

Assessment serum OVA-specific IgE and cytokine levels

The serum OVA-specific IgE, IL-4 and IFN-γ levels measured by a double-antibody sandwich enzyme-linked immunosorbent assay kits, manufactured by SunRed Bio. Tech., Shanghai, China, according to the manufacturer's instructions, with minimum detection limits of 6.5 ng/l, 8 ng/l, and 5 ng/l respectively. All optical densities analyzed at 450 nm using an automated ELISA plate reader, Stat Fax-2100, Fisher Bioblock Scientific, France, and expressed as ng/l.

Histopathological changes assessment

Tissue samples processed, and 5 μm sections stained with hematoxylin and eosin, for assessment of histopathological changes, and toluidine blue, for identification of mast cells. The number of total and degranulated mast cells counted in 5 fields (×400) manually [38,39].

Immunohistochemical CD4⁺ expression

The intestinal tissues assessed for the intensity of CD4⁺ immunohistochemical expression. Where, the expression, arbitrary semi-quantified as follows, 0, negative reaction, 1, <10%, 2, 10–50% and 3, >50% of cells showed positive reaction [40].

Statistical analysis

For assessment of the statistical difference between two groups, either the two-sample Student's *t*-test or the Mann-Whitney's *U*-test used, after evaluation of the data's variances using an F-test. Moreover, for assessment of the statistical difference between multiple groups, either one-way ANOVA (followed by Tukey's test as a *post-hoc* test) or Kruskal-Wallis's test (followed by Mann-Whitney's *U*-test as a *post-hoc* test) used, after analysis of the data variances using Bartlett's test. Data expressed as mean ± SD, and a *p*-value of less than 0.05 considered significant.

Results

FA manifestations

Rectal temperature change

OVA-sensitization and repeated challenge decreased the rectal temperature significantly than the control group. However, the treatment with both fisetin and telmisartan significantly restored the rectal temperature with no significant difference in between. Furthermore, the treatment with the low-dose combination regimen was as significant as dexamethasone, fisetin high-dose, and telmisartan high-dose therapies. Additionally, it significantly enhanced the rectal temperature than the low-dose fisetin and telmisartan therapies each alone (Fig. 1).

Diarrheal score

The OVA-group exhibited a significant elevation of the diarrheal score as compared to the control group. Nevertheless, fisetin and telmisartan therapies dose-dependently suppressed the elevated diarrheal score, with a nonsignificant difference in between.

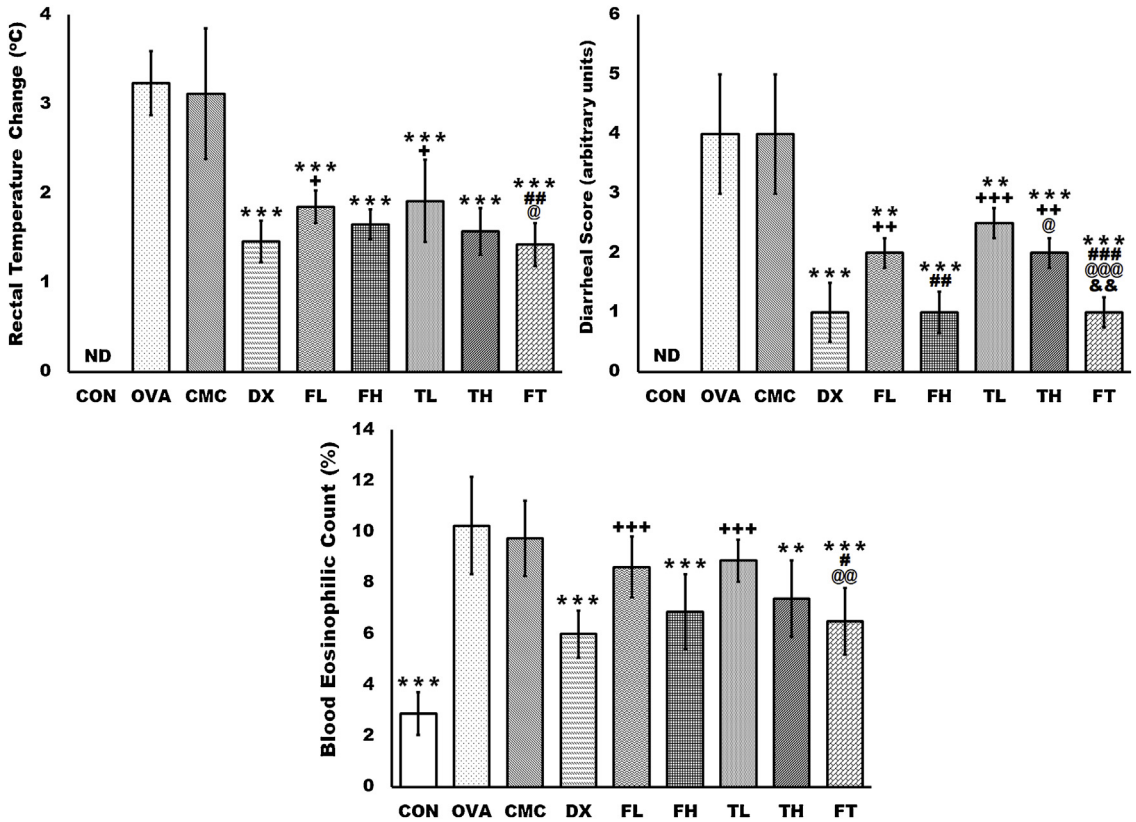

Fig. 1. Effect of fisetin and/or telmisartan on FA manifestations and blood eosinophilic count. ND, no difference, $^{**}p < 0.01$, $^{***}p < 0.001$ (*vs.* OVA-group), $+p < 0.05$, $++p < 0.01$, $+++p < 0.001$ (*vs.* DX-group), $\#p < 0.05$, $\#\#p < 0.01$, $\#\#\#p < 0.001$ (*vs.* FL-group), $@p < 0.05$, $@@p < 0.01$, $@@@p < 0.001$ (*vs.* TL-group) and $\&\&p < 0.01$ (*vs.* TH-group).

Moreover, the dexamethasone treatment reduced it significantly, in comparison to the high-dose telmisartan treatment; however, it was as significant as the high-dose fisetin therapy in the reduction of the diarrheal score. In addition, the low-dose combination therapy showed a significant reduction in the diarrheal score in comparison to the low-dose fisetin, low-dose, and high-dose telmisartan therapies; it was as significant as the high-dose fisetin and dexamethasone therapies (Fig. 1).

Blood eosinophilic count

The treatment with both fisetin and telmisartan dose-dependently reduced the blood eosinophilic count, elevated by OVA-sensitization and repeated challenge, with a nonsignificant difference in between. Moreover, the dexamethasone and the low-dose combination therapies showed no significant difference with them. However, the low-dose combination therapy significantly reduced it than the low-dose fisetin and telmisartan each alone (Fig. 1).

Serum parameters

OVA-sensitization and repeated challenge elevated significantly the serum OVA-specific IgE and IL-4 levels and reduced the serum IFN-γ level as compared to the control group. However, the treatment with fisetin and telmisartan effectively reduced the raised serum levels of OVA-specific IgE and IL-4 in a dose-dependent manner, and enhanced the reduced serum IFN-γ level, with no significant difference in between. Additionally, there was no significant difference between the high-dose fisetin and high-dose telmisartan, dexamethasone and low-dose combination therapies in the reduction of the serum levels of OVA-specific IgE and IL-4, and in the promotion of the serum IFN-γ level. Yet, the dexamethasone and low-dose combination treatments suppressed serum IL-4 level than the high-dose telmisartan therapy. Furthermore, the low-dose combination therapy reduced serum OVA-specific IgE and IL-4 levels, and increased serum IFN-γ level than the low-dose fisetin and telmisartan each alone, (Fig. 2).

Histopathological changes

Hematoxylin and eosin staining

The repeated OVA challenge induced a severe allergic intestinal inflammation, manifested by severe intestinal mononuclear cell infiltration and edema, with irregular distortion of the intestinal villi, as compared to the normal intestinal architecture in the control group. Nonetheless, the treatment with both fisetin and telmisartan dose-dependently restored the normal histological picture of the intestine, as revealed by mild intestinal inflammatory infiltration seen in the FL, TL, and TH-groups. Moreover, the FH and FT-groups showed a nearly normal pattern of the intestinal villi, with few mononuclear cell infiltrations (Fig. 3).

Mast cells count

The repeated OVA challenge significantly increased the total and the degranulated intestinal mast cell count, when compared to the control group. In contrary, the treatment with both fisetin and telmisartan dose-dependently reduced the increased counts, with no significant difference in between. Furthermore, there is no significant difference between the high-dose fisetin and telmisartan each alone, the low-dose combination and dexamethasone therapies in the reduction of mast cell counts. However, the low-dose combination therapy significantly reduced them than the low-dose fisetin and telmisartan each alone (Figs. 4 and 6).

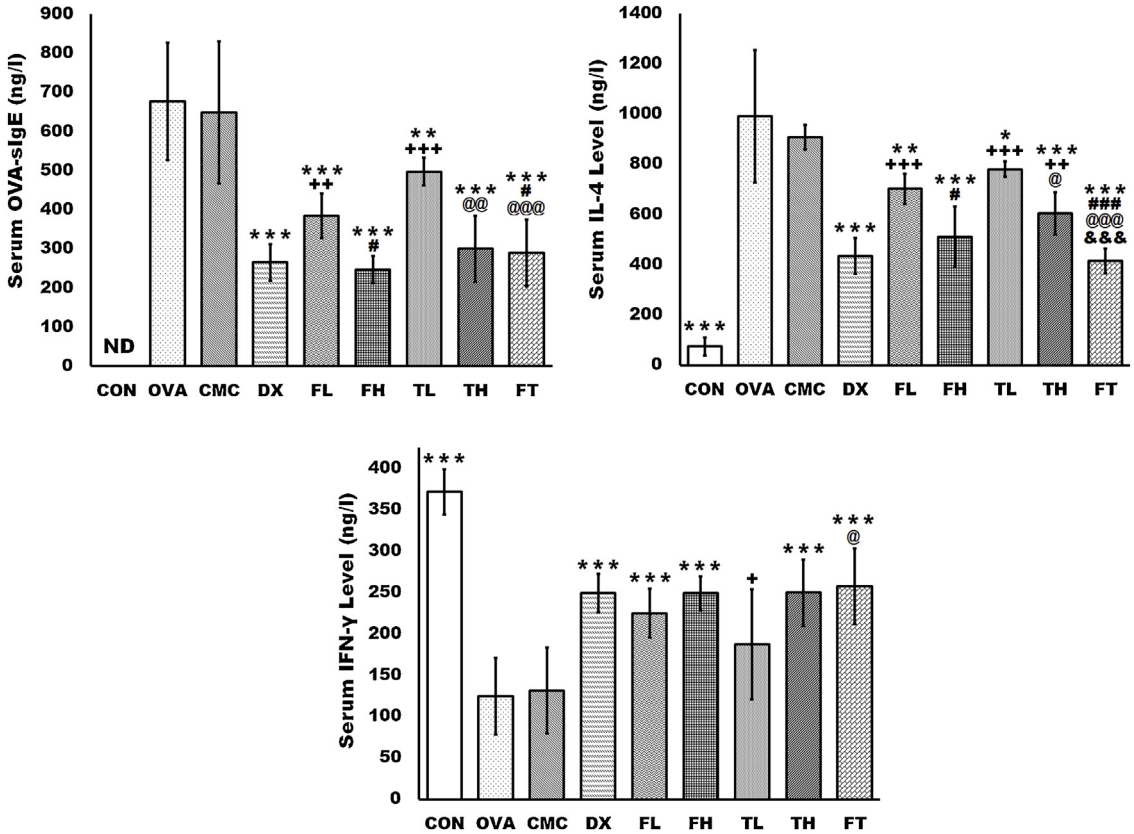

Fig. 2. Effect of fisetin and/or telmisartan on serum OVA-specific IgE and cytokine levels. ND, not detected, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ (*vs.* OVA-group), $+p < 0.05$, $++p < 0.01$, $+++p < 0.001$ (*vs.* DX-group), $\#p < 0.05$, $\#\#\#p < 0.001$ (*vs.* FL-group), $@p < 0.05$, $@@p < 0.01$, $@@@p < 0.001$ (*vs.* TL-group) and &&& $p < 0.001$ (*vs.* TH-group).

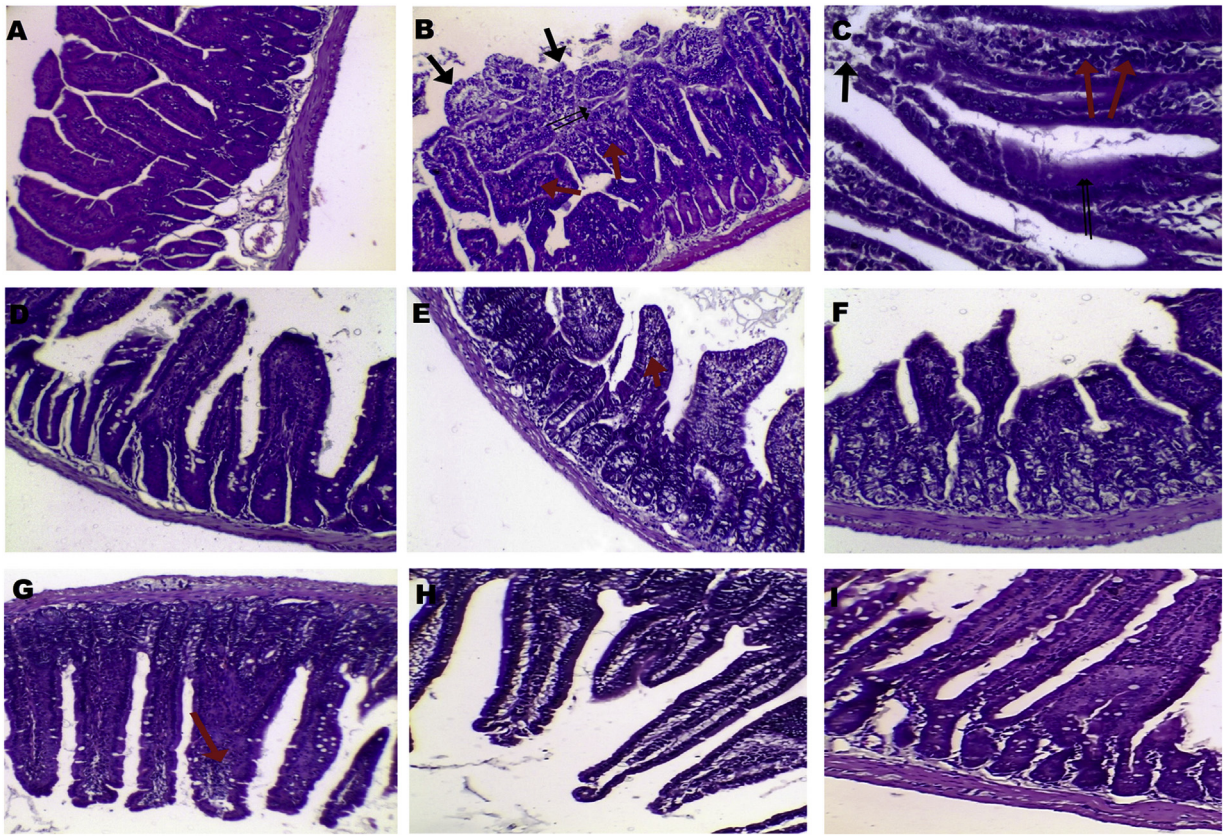

Fig. 3. Effect of fisetin and/or telmisartan on intestinal histopathological changes. A, CON-group. B, OVA-group. C, CMC-group. D, DX-group. E, FL-group. F, FH-group. G, TL-group. H, TH-group. I, FT-group. Black arrow, distorted intestinal villi, red arrow, inflammatory infiltrates mainly by lymphocytes and eosinophils, and double black arrows, villi edema (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

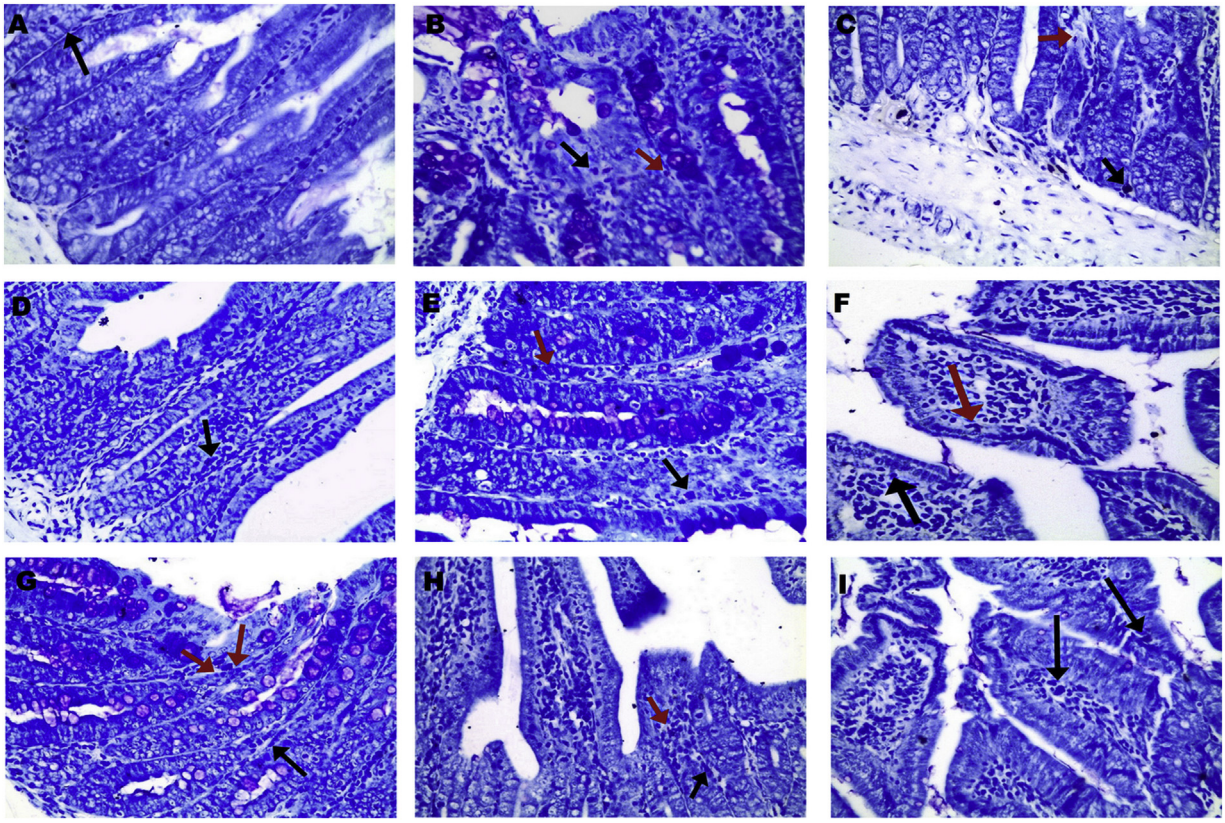

Fig. 4. Effect of fisetin and/or telmisartan on intestinal total and degranulated mast cells. A, CON-group. B, OVA-group. C, CMC-group. D, DX-group. E, FL-group. F, FH-group. G, TL-group. H, TH-group. I, FT-group. Black arrow, intact mast cell, and red arrow, degranulated mast cell (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Immunohistochemical CD4⁺ expression

The repeated OVA challenge significantly increased the intestinal CD4⁺ immunohistochemical expression as compared to the control group. The treatment with fisetin and telmisartan significantly and dose-dependently suppressed its expression, with no significant difference in between. Moreover, there was non-significant difference between the high-dose fisetin, the dexamethasone, and the low-dose combination therapies in its suppression. Additionally, the low-dose combination therapy significantly inhibited its expression than the low-dose fisetin, the low-dose, and the high-dose telmisartan therapies each alone (Figs. 5 and 6).

Discussion

The data of the present study revealed that the oral treatment with fisetin and telmisartan each alone or in low-dose combination attenuated the OVA-induced FA in mice. This revealed by reduction of the rectal temperature change and diarrheal score, elevated blood eosinophilic count, serum OVA-specific IgE, and IL-4 levels, intestinal total and degranulated mast cells count, and CD4⁺ immunohistochemical expression. In addition, they enhanced serum IFN-γ level and abrogated the intestinal histopathological changes induced by the OVA. Furthermore, the low-dose dose combination therapy was as powerful as the high-dose fisetin and telmisartan each alone in attenuation of the FA, except for the diarrheal score, serum IL-4 level, and intestinal CD4⁺ immunohistochemical expression, where the low-dose combination therapy was powerful than the high-dose telmisartan therapy.

In fact, the imbalance of Th1/Th2 cytokine secretion, with dominance of Th2 cytokine secretion and suppression of Th1 cytokine secretion ends ultimately in IgE-mediated allergic reaction development, including FA [2,3]. Where, IL-4, the major Th2 cytokine, induces B-cells growth, proliferation, and IgE-secreting plasma cells differentiation [41]. Furthermore, it enhances mast cell differentiation, activation, and degranulation, with promotion of eosinophil adhesion to vascular endothelial cells, consequently, inflammatory sites infiltration, where it secretes IL-4 autocrinally, thus amplifies the local inflammatory reactions, with subsequent augmentation of FA manifestation [1,3]. Additionally, IL-4 enhances intestinal mast cell infiltration and degranulation, hence, the release of leukotrienes and histamine, with the development of FA anaphylactic manifestation [3,31,35]. Furthermore, IL-4 knockout mice were unable to develop FA anaphylactic manifestations and OVA-specific IgE, after OVA sensitization and repeated challenge [42].

In contrary, IFN-γ, the principle effector Th1 cytokine, suppresses FA, especially which mediated by IgE, through repression of antigen presentation to T cells, Th2 cell differentiation and cytokine secretion, recruitment of inflammatory cells, and B-cells IgE-isotype switch. Additionally, it induces Th2, mast cells, and eosinophils apoptosis, and enhances Th1 phenotype differentiation and cytokine secretion [1,3].

In the present study, administration of fisetin, telmisartan each alone or in low-dose combination in OVA-induced FA, suppressed the elevated serum level of IL-4, and enhanced the reduced serum level of IFN-γ, indicating the restoration of normal Th1/Th2 cytokine balance. Subsequently, they repressed OVA-specific IgE production, mast cell mucosal infiltration, activation, degranulation, thus inhibited the anaphylactic manifestation and the intestinal histopathological changes associated with FA. Moreover, the oral bioavailability of fisetin is 7.8% however, the present study revealed that fisetin was effective in such low levels. This could

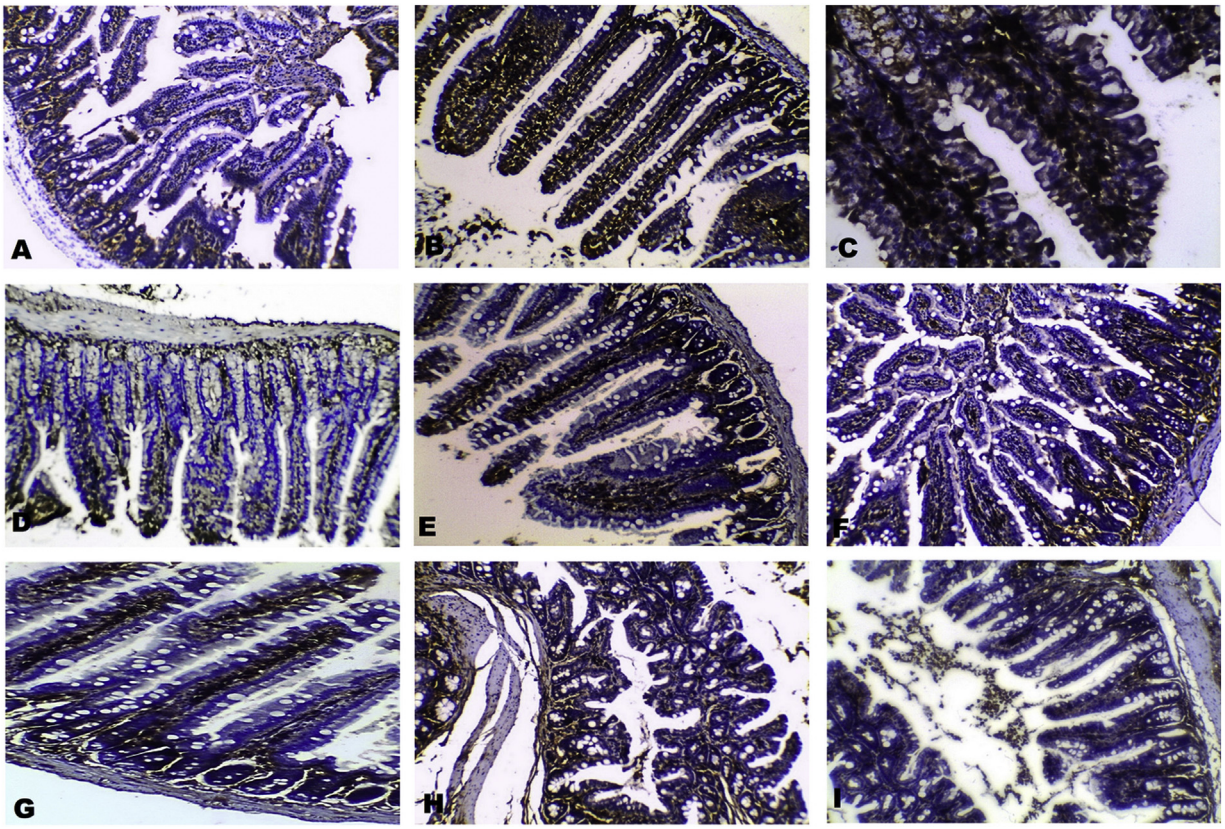

Fig. 5. Effect of fisetin and/or telmisartan on the intestinal CD4⁺ immunohistochemical expression of OVA-induced FA in BALB/c mice. A, CON-group. B, OVA-group. C, CMC-group. D, DX-group. E, FL-group. F, FH-group. G, TL-group. H, TH-group. I, FT-group.

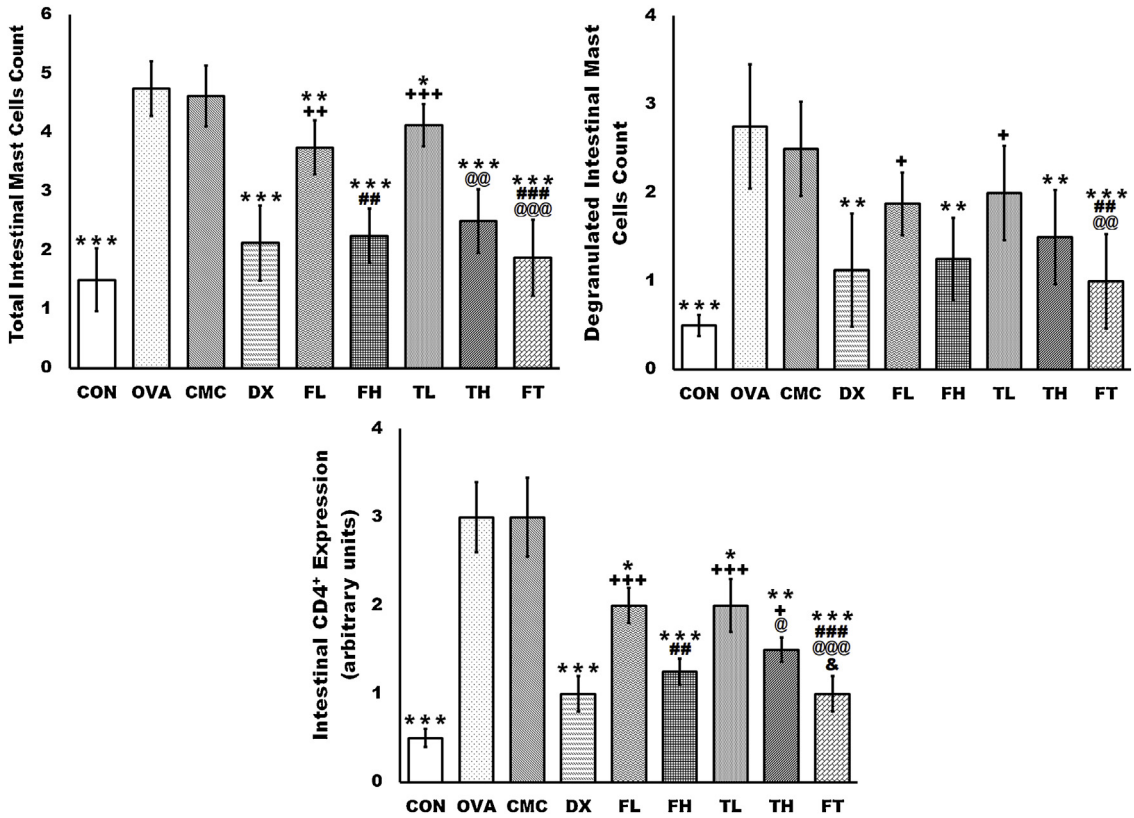

Fig. 6. Effect of fisetin and/or telmisartan on intestinal total and degranulated mast cell count, and CD4$^+$ immunohistochemical expression. Results expressed as mean ± SD of 8 mice per each-group. ND, not detected, $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ (*vs*. OVA-group), $+p < 0.05$, $++p < 0.01$, $+++p < 0.001$ (*vs*. DX-group), $\#\#p < 0.01$, $\#\#\#p < 0.001$ (*vs*. FL-group), $@p < 0.05$, $@@p < 0.01$, $@@@p < 0.001$ (*vs*. TL-group) and $\&p < 0.05$ (*vs*. TH-group).

explained by the 2 h animal fast before the fisetin administration, thus decreasing the effect of gut contents on bioavailability [34].

Matching with our data, fisetin exhibited potent anti-inflammatory and immunomodulatory potentialities in different allergic animal models and clinical trials [43]. Where, fisetin explicated a potent anti-allergic effect of in OVA-induced bronchial asthma in mice, due to its ability to suppress Th2 cell differentiation and cytokine secretion, and inhibition of nuclear factor- kappa B (NF-κB) and its downstream chemokines. Thus, reducing the elevated IL-4, and eosinophils infiltration, with amelioration of eosinophilic airway inflammation [23,24]. Moreover, fisetin reported to suppress Th2 type cytokine, IL-4, and IL-5 expression, and nuclear translocation of NF-κB by anti-IgE antibody-stimulated human basophils in response to cross-linking with IgE receptors hence suppressed the allergic reaction [44]. Furthermore, fisetin inhibited allergic inflammatory reactions, *via* suppression of mast cell activation due to the interference of cell-to-cell interaction, and repression of NF-κB and MAPKs cascades. Therefore, it inhibited mast cells IgE-mediated histamine and leukotrienes release, and Th2 inflammatory cytokine types secretion [45,46].

Likewise, telmisartan has exposed powerful direct and indirect anti-inflammatory and immunomodulatory activities, through inhibition of inflammatory cytokine secretion, eosinophilic recruitment, and DCs activation, meanwhile, stimulation of PAPR-γ [5,7,30]. Telmisartan reported to alleviate OVA-induced allergic airway inflammation in rodents, *via* blockade of AT1 and stimulation of PPAR-γ receptors, thus reduced airways and blood eosinophilic count, serum OVA-specific IgE level, and inhibited airways remodeling [8,47]. Moreover, telmisartan inhibits DCs, *via* stimulation of PPAR-γ, thus suppresses eosinophilic airway inflammation development [30]. Additionally, angiotensin II stimulates AT1 receptor, hence activation of the NF-κB cascade, thus activates mast cells, T lymphocytes and macrophages [48]. Furthermore, angiotensin II secreted autocrinally, with augmentation of local inflammatory cytokines, chemokines, and cell adhesion molecule secretion, consequently further infiltration of inflammatory cells, with allergic inflammation amplification [7,49]. Thus, the blockage of the AT1 receptor prevents mast cell and T lymphocyte differentiation, recruitment, and activation, with consequent suppression of the allergic inflammatory reactions [50].

Furthermore, we believed that the effect of the low-dose combination therapy due to the fisetin additive effect to telmisartan activities, since fisetin modulates the OVA-induced FA *via* its potent anti-allergic, anti-inflammatory, and immunomodulatory capabilities, however, telmisartan improved allergic intestinal inflammation *via* AT1 receptors blockade and its agonistic activities on PAPR-γ [5,7,23,24,30].

Conclusion

In conclusion, both fisetin and telmisartan each alone or in low-dose combination exerted potent anti-inflammatory and immunomodulatory activities, thus abled them to alleviate OVA-induced FA in mice. This alleviation believed to be due to their capability to restore the normal Th1/Th2 cytokine balance and AT1 blockade-activity. Therefore, either fisetin, telmisartan or their low-dose combination could be promising in the management of FA.

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Declarations of interest

The authors declare that they have no conflicts of interest.

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