Piceatannol, a stilbene present in grapes, attenuates dextran sulfate sodium-induced colitis

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ARTICLE INFO

Article history:
Received 1 July 2008
Received in revised form 5 August 2008
Accepted 7 August 2008

Keywords:
Inflammatory bowel disease
Piceatannol
Inflammation
Dextran sulfate sodium
Cytokines

ABSTRACT

Piceatannol (3,5,3’,4’-tetrahydroxy-trans-stilbene; PIC) is a polyphenol found in grapes. It is known as a protein kinase inhibitor that modifies multiple cellular targets, exerting immunosuppressive and antitumorigenic activities in several cell lines. The purpose of the present work was to evaluate the anti-inflammatory effect of PIC on dextran sulfate sodium (DSS)-induced colitis. Experimental colitis was induced in BALB/c mice by dissolving 5% DSS in their drinking water for 7 days. PIC (1, 2.5, 5, or 10 mg/kg body weight) was administrated daily per oral route for 7 days. A significant blunting of weight loss and clinical signs was observed in DSS-exposed, PIC-treated mice when compared to vehicle-treated mice. This was associated with a remarkable amelioration of the inflammatory effect of PIC.

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1. Introduction

Piceatannol (3,5,3’,4’-tetrahydroxy-trans-stilbene; PIC) is a polyphenol found in grapes, Rheum undulatum, rhubarb, and sugar cane. It is known as a protein kinase inhibitor that modifies multiple cellular targets, exerting immunosuppressive and antitumorigenic activities in several cell lines [1–4]. PIC was originally reported to be a Syk/ZAP70-specific kinase inhibitor [2]. By inhibiting Syk/ZAP70-specific kinase activities, PIC attenuates antigen-induced anaphylactic bronchial smooth muscle contraction and suppresses the release of histamine and peptidoleukotrienes from lung fragments isolated from sensitized guinea pigs [3]. Moreover, PIC strongly inhibits TNF-induced nuclear factor (NF)-κB activation in myeloid cells, lymphocyte and epithelial cells without Syk/ZAP70-specific kinase activity [4], and selectively inhibits the tyrosine phosphorylation of signal transducer and activator of transcription (STAT)3 in human T and B cells [5]. Although PIC has been shown to exert various pharmacological effects on immune and cancer cells in vitro, the in vivo evidences are sparse.

Inflammatory bowel disease (IBD) is a group of pathologic conditions of the gastrointestinal tract in humans, of which Crohn’s disease (CD) and ulcerative colitis (UC) are the most prominent [6]. Although the etiology of IBD still remains unclear, it has been suggested that inflammatory and immune responses play major roles in the pathogenesis [7,8]. A common feature of IBD is a complex interplay of cells and inflammatory mediators such as cytokines within the intestine [8,9]. Interaction of a cytokine with its specific receptor initiates signals that modify cell function in both the cytoplasm and the nucleus. STAT proteins are a family of regulatory elements participating in this process. After activation by a family of cytoplasmic tyrosine kinases termed Janus kinases (JAK), which are associated with cell surface cytokine receptors, STATs translocate into the nucleus [10,11]. Previous investigation has demonstrated that strongly activated states of STAT3 are found in patients with IBD and in animal models of colitis [12]. These findings have been confirmed in additional studies of human IBD [13]. Serum concentrations of interleukin (IL)-6, a potent mediator of STAT3 activation, have been shown to be augmented in patients with IBD [14,15]. Recent studies have demonstrated the benefit of antibodies against the IL-6 receptor in patients with Crohn’s disease [16], as well as in animal models of colitis [17,18]. These data strongly suggest that activation of the IL-6/STAT3 pathway plays a key role in the development of IBD.

These observations led us to examine the effect of PIC on intestinal inflammation. It has been reported that PIC impairs activation of NF-κB and STAT-3 in various cell lines, and we were interested in determining if PIC has a therapeutic effect on inflammation by reducing NF-κB and STAT-3 activation [4,5]. In order to investigate the effects of PIC, we studied a dextran sulfate sodium (DSS)-induced mouse colitis model. This model resembles human IBD and is used for pharmacological...
2. Materials and methods

2.1. Synthesis of PIC

We synthesized PIC (Fig. 1A) in 6 steps from 3,5-dihydroxybenzoic acid by using Wittig–Horner reaction as described at Fig. 1B.

2.2. Mice and experimental protocol

The study protocol was approved by the Animal Care and Use Committee of Hallym University. Six-week-old female BALB/c mice were purchased from Japan SLC (Hamamatsu, Japan) and maintained under specific pathogen-free conditions at the animal facility of Hallym University (Chuncheon, Korea). To induce experimental colitis, the mice were treated for 7 days with 5% DSS (40,000–50,000 MW; ICN Biomedicals, Aurora, OH, USA) dissolved in filter-purified water (Millipore Corp, Bedford, MA, USA). The control mice received filter-purified water alone. PIC was dissolved in dimethyl sulfoxide (DMSO) and was freshly diluted in corn oil. PIC (1, 2.5, 5, or 10 mg/kg of body weight) or the vehicle (corn oil with DMSO) was administered by gavage for 7 days, beginning in coordination with the start of DSS exposure. We did not observe differences in water consumption among the groups (3.5–4.0 ml/day/mouse) during the experimental period. The study protocol was approved by the Animal Care and Use Committee of Hallym University.

2.3. Assessment of DSS-induced colitis

The mice were assessed daily for the development of colitis based on body weight, gross rectal bleeding, stool consistency, and survival. Overall disease severity was assessed using a clinical scoring system with a scale of 0–4 [19].

2.4. Colon tissue culture

Tissue from the mid-colon was washed with RPMI 1640 (Hyclone, Logan, UT, USA) medium containing 2% fetal bovine serum (FBS, Hyclone) and penicillin and streptomycin (Hyclone) before being cut into smaller pieces. Then, approximately 0.5 cm of tissue was placed in 0.5 ml of 0.1% FBS containing RPMI-1460 medium, loaded in 48-well tissue culture plates, and incubated for 24 h at 37 °C in 5% CO2.

2.5. Measurement of cytokines, NO, and PGE2

Concentrations of various cytokines in the cell-free culture supernatants of the colon tissues were measure using a Bio-Rad Multiplex bead array instrument and cytokine kit (Bio-Rad, Irvine, CA, USA), according to the manufacturer’s protocol. Nitrite and PGE2 production were measured using the Griess reagent system (Promega, Madison, WI, USA) and an enzyme-linked immunosorbent assay (ELISA) kit from R&D Systems (Minneapolis, MN, USA), respectively, according to the manufacturer’s instructions.

2.6. Determination of myeloperoxidase (MPO) activity in the colon

The mouse colons (50-100 mg) were rinsed with cold PBS, blotted dry, and immediately frozen in liquid nitrogen. They were then stored at −80 °C until they were assayed for MPO activity using the o-dianisidine method [22].

2.7. Quantitative real time RT-PCR

The total RNA from the 100 mg of colon homogenates was isolated using an RNAeasy mini kit (Quiaeng, Hilden, Germany). After RNA
preparation, the cDNA was transcribed using a single reverse transcriptase synthesis step with Superscript reagents (Invitrogen, Carlsbad, CA, USA). Quantitative PCR was performed, with the incorporation of SYBR green into the double-stranded PCR products. The primers used in quantitative PCR were as follows: iNOS, forward 5′-CAT TGG AAG TGA AGC GTT TCG-3′ and reverse 5′-CAG CTG GGC TGT ACA AAC C-3′; COX-2, forward 5′-TTC AAA AGA AGT GGG GAA AAG G-3′ and reverse 5′-GAT CAT CTC TAC CTG AGT GTC-3′; IL-6, forward 5′-GAG GAT ACC ACT CCC AAC AGA CC-3′ and reverse 5′-TGC ATC ATC GTT GTC-3′; IL-10, forward 5′-GGT TGC CAA GCC TTA TCG G-3′ and reverse 5′-ACC ACC ACT CCC AAC AGA CC-3′ and reverse 5′-GAG TAT ACC TTC ACT GCC TTG C-3′; TNF-α, forward 5′-CAT TTC CTC AAA ATT CGA GTG AC-3′ and reverse 5′-TGC GAG TAG ACA AGG TAC-3′; interferon (IFN)-γ, forward 5′-ATC TGG AGG AAC TGG CAA-3′ and reverse 5′-GCA GTG CAT TGA AGT CTC TTG G-3′; monocyte chemoattractant protein-1 (MCP-1), forward 5′-AGG GCC AGC GCC AGC TCT CTC TCT CTC-3′ and reverse 5′-CTG AGC AGC AGG ACA GAC-3′; keratinocyte chemoattractant (KC), forward 5′-CTT GAA GGT GTT GCC CTC AG-3′ and reverse 5′-TGG GGA CAC CTT TTA GCA TC-3′; β-actin, forward 5′-AGA GGG AAA TCG TGC GTG AC-3′ and reverse 5′-CAA TAG TGA TGA CCT GGC CGT-3′. The specificity of the reaction was tested via product separation using protein gel electrophoresis, or via melting curve analysis when SYBR green was incorporated. The mean relative expressions of the cytokine genes were calculated, and differences were determined using the 2−ΔC(t) method.

2.8. Immunohistochemical study

The colonic tissues were fixed in 4% buffered paraformaldehyde, dehydrated through graded concentrations of ethanol, embedded in paraffin, and sectioned. The sections (5 μm thick) were mounted on slides, then cleared and hydrated; all sections were treated with a buffered blocking solution (3% BSA) for 15 min. The sections were then co-incubated with primary antibodies for NF-κB p65 (Cell Signaling Technologies, Beverly, MA, USA) or phospho-STAT3 (Cell Signaling Technologies) at a dilution of 1:100 at room temperature for 1 h. Next, the sections were washed with PBS and co-incubated with a secondary antibody of peroxidase conjugated anti-sheep IgG (1:500 in PBS, v/v)
at room temperature for 1 h. Thereafter, the sections were washed as before with 0.05 M Tris–HCl, pH 7.66, and then co-incubated with 3,3′-diaminobenzidine solution in the dark at room temperature for 10 min. Finally, the sections were washed with Tris–HCl and stained with haematoxylin according to standard protocols.

2.9. Statistical analysis

The data are presented as means±SEM from three independent experiments. Figures were evaluated using one-way ANOVA, followed by Duncan’s multiple range tests. GraphPad Prism 4.0 software (GraphPad Software Inc., San Diego, CA, USA) was used for all calculations. A P<0.05 was considered statistically significant.

3. Results

3.1. Synthesis of PIC

It was reported that 0.3 g of pure PIC was isolated from 1 kg of dry root of *Rheum undulatum* [23]. Since the limited supply of PIC from nature, we synthesized of PIC in 6 steps from 3,5-dihydroxybenzoic acid by using Wittig–Horner reaction (Fig. 1B). 3,5-dihydroxybenzoic acid (2, Fig. 1B) in acetone at reflux with benzyl bromide and potassium carbonate produced 97% yield of benzylated ester 3 which was then reacted with LiAlH₄ in THF at room temperature to give benzylalcohol 4 in 88% yield. Bromination of 4 with PBr₃ in acetonitrile at room temperature yielded 5 in 99% yield. Phosphonation of 5 with

**Fig. 3.** Reduced (A) STAT-3 and (B) NF-κB activation in piceatannol (PIC)-treated colon. Colonic tissue from dextran sulfate sodium (DSS)-exposed PIC-treated mice and DSS-exposed control mice were prepared and immunostained with antibodies against (A) phospho-STAT3 and (B) the p65 subunit of NF-κB, as described in the Materials and methods section. Original magnification ×100 (upper panel) and ×200 (lower panel).
triyethyl phosphate in xylene at reflux afforded 92% yield of 5. Wittig–Horner reaction of 6 with benzylated vanillin 7 by using NaH in THF at reflux gave only the desired (E)-stilbene 6 in 99% yield. Finally, dealkylation of 7 by BBr3 in methylene chloride at room temperature gave PIC in 50% yield. Finally, the 6 steps reaction procedure including benzylation, reduction, bromination, phosphonation, Wittig–Horner reaction, and dealkylation gave PIC in 38% overall yield.

3.2. Body weight, clinical symptoms, colon length and histopathological analysis

We began monitoring symptomatic colitis parameters such as weight loss and disease activity index (DAI) 10 days after starting oral 5% DSS administration; Fukuta et al. [24] previously reported that the degree of epithelial damage was most severe between days 8 and 11 after DSS was given. PIC (2.5–10 mg/kg) treatment reduced weight loss in mice with colitis as shown in Fig. 2A. Another common feature of DSS-induced colitis is an increase in the DAI [4]. In this study, the DAI decreased significantly in the mice receiving PIC (2.5–10 mg/kg) compared with the mice receiving vehicle treatment (Fig. 2B). Colon lengths were significantly decreased in the colitis mice because of mucosal inflammation, edema, and thickening [2,3]. This decrease in colon length was significantly attenuated in 2.5–10 mg/kg PIC-treated mice at day 10 following DSS treatment, a finding which was consistent with the observations related to weight loss and DAI index (Fig. 2C). However, low concentration of PIC (1 mg/kg) failed to reverse the general symptoms of colitis.

We undertook histological examination of the colonic sections to assess intestinal inflammatory status. Microscopically, samples from the DSS-induced colitis mice showed typical inflammatory changes in colonic architecture, such as ulceration, crypt dilation, and goblet cell depletion, as well as a mixed cell infiltration composed mainly of macrophages, lymphocytes, plasma cells, and granulocytes. Conversely, histological analysis of the colons from PIC-treated mice showed greatly reduced cell infiltration, mucosal injury, and edema (Fig. 2D).

3.3. STAT-3 and NF-κB immunohistochemistry

Next, we examined the effect of PIC on the activation of STAT-3 and NF-κB in the colon, because PIC has been reported to be an inhibitor of STAT-3 and NF-κB activation [4,5]. In the control non-colitic animals, only weak immunoreactivity was detected for phospho-STAT3 and the p65 subunit of NF-κB in the apical cytoplasm of ileal villous enterocytes (Fig. 3). In animals that were selected 10 days after DSS administration, marked phospho-STAT3 and NF-κB immunoreactivity were evident throughout the nuclei of the epithelial cells. Administration of PIC 10 mg/kg significantly decreased the translocation of phospho-STAT3 and of the p65 subunit of NF-κB to enterocyte nuclei when compared with the DSS-treated group.

3.4. MPO activity and production of inflammatory mediators in colonic tissues

MPO is an enzyme produced mainly by polymorphonuclear leukocytes, and it is associated with the degree of neutrophil infiltration in a given tissue. Following 10 days of DSS treatment, MPO activity became markedly increased, to a level approximately 13 times higher than that in the control group (Fig. 4A). This increase in MPO activity was significantly reduced by PIC administration. High concentration (10 mg/kg) PIC treatment suppressed the MPO activity to basal level. Since MPO activity is considered a biochemical marker of neutrophil infiltration [22], this result suggests that PIC exerts anti-inflammatory effects by reducing neutrophil infiltration into the colonic mucosa.

NO and PGE2 are considered important inflammatory mediators playing a key role in the pathogenesis of IBD [25,26]. For this reason, we also evaluated the effect of PIC on colonic NO and PGE2 production in the DSS-induced colitis mice. As shown in Fig. 4B and C, DSS administration produced increased levels of NO and PGE2. However, oral administration of PIC reduced NO and PGE2 production in a concentration-dependent manner at day 10.

To determine the effect of PIC on major inflammatory cytokine production in the colon, the IL-1β, IL-6, TNF-α, and IL-10 levels were determined (Table 1). After 10 days of DSS administration, the IL-1β, IL-6, and TNF-α levels had increased significantly to 1254±262, 3075±739, and 50.4±10.8 pg/mg of protein, respectively. This contrasted with the control group IL-1β, IL-6, and TNF-α levels of 91.8±0.8, 52.6±23.3, and 5.8±0.7 pg/mg of protein, respectively. PIC administration (10 mg/kg) prevented significant increases in IL-1β, IL-6, and TNF-α levels, which were 94.9±1.9, 42.4±3.6, and 2.9±0.5 pg/mg of protein,

Table 1

Effects of piceatannol of the production of colonic inflammatory cytokines and chemokines in dextran sulfate sodium (DSS)-induced colitis mice

<table>
<thead>
<tr>
<th></th>
<th>IL-1β (pg/mg protein)</th>
<th>IL-6 (pg/mg protein)</th>
<th>TNF-α (pg/mg protein)</th>
<th>IL-10 (pg/mg protein)</th>
<th>MCP-1 (pg/mg protein)</th>
<th>KC-1 (pg/mg protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBS</td>
<td>91.7 ± 11</td>
<td>52.6 ± 23.6</td>
<td>5.8 ± 0.3</td>
<td>59.6 ± 2.8</td>
<td>941.4 ± 71.3</td>
<td>794.8 ± 215.0</td>
</tr>
<tr>
<td>DSS</td>
<td>12540 ± 262.5</td>
<td>3075 ± 739.4</td>
<td>50.4 ± 10.8</td>
<td>137.9 ± 16.4</td>
<td>60110 ± 2745.0</td>
<td>4352.9 ± 1792.3</td>
</tr>
<tr>
<td>DSS + PIC-2.5</td>
<td>1858 ± 473.2</td>
<td>2638 ± 775.6</td>
<td>73.7 ± 12.5</td>
<td>75.7 ± 27.3</td>
<td>6130 ± 1592.7</td>
<td>4772.7 ± 1791.1</td>
</tr>
<tr>
<td>DSS + PIC-5</td>
<td>6118 ± 154.0</td>
<td>8975 ± 146.4</td>
<td>60.4 ± 26.2</td>
<td>109.4 ± 32.8</td>
<td>32681 ± 943.6</td>
<td>3970.8 ± 782.3</td>
</tr>
<tr>
<td>DSS + PIC-10</td>
<td>94.9 ± 1.2 **</td>
<td>42.4 ± 3.7 ***</td>
<td>271 ± 0.1 ***</td>
<td>78.8 ± 5.6</td>
<td>305.6 ± 203.9 **</td>
<td>592.1 ± 88.5 **</td>
</tr>
</tbody>
</table>

**Segments of colon from DSS-administered, PIC-treated mice and from DSS-treated control mice were prepared on day 10 after DSS exposure and cultured without any stimulation for 24 h at 37 °C. Values are means ± SEM. Significant differences in the DSS group, *P < 0.05, **P < 0.01 and ***P < 0.001."
respectively, at day 10. However, the level of IL-10 was not significantly altered by PIC treatment.

We also investigated the effect of PIC on inflammatory chemokine production. Inflammatory chemokines direct immune cells to local sites of inflammation. Each chemokine attracts specific cells. For instance, MCP-1 contributes to monocyte recruitment, while KC is specific to neutrophil recruitment, and each plays a crucial role during inflammation. Although less than 5 mg/kg of PIC treatment did not inhibit MCP-1 or KC production, 10 mg/kg of PIC dramatically reduced MCP-1 and KC production in the colon (Table 1). This indicates that PIC exerts anti-inflammatory effects by reducing monocyte and neutrophil infiltration into the colonic mucosa.

3.5. mRNA expression of inflammatory mediators in colonic tissues

To provide further insight into the molecular mechanisms underlying the suppression of colitis by PIC, mRNA expression levels of iNOS, COX-2, inflammatory cytokines, and chemokines in the colon were measured by real-time RT-PCR. As shown in Fig. 5A, mRNA levels for iNOS and COX-2 were significantly induced 10 days after the start of DSS exposure. The increases in iNOS and COX-2 were attenuated by 85% and 69%, respectively, after PIC administration (10 mg/kg). DSS-induced mRNA expression of IL-6 and TNF-α also decreased in PIC-treated colon. In consistence with the production of IL-10, Colonic IL-10 mRNA expression was not changed by PIC treatment (Fig. 5B). Treatment of DSS-fed mice with PIC caused a significant attenuation of MCP-1 and KC mRNA expression, which was parallel to the attenuation of protein expression (Fig. 5C).

4. Discussion

PIC has previously been reported to attenuate LPS-induced inflammatory reactions in murine macrophage RAW264.7 cells [27] and BV2 microglia [28] via inactivation of NF-κB signal transduction. In addition, PIC is a promising chemopreventive agent with anti-leukemic activity. It has been extensively studied for the treatment of various diseases, including bladder cancer, lung cancer, and cardiovascular disease [1,29,30]. However, previous chemopreventive studies have presented scant experimental data and have used in vitro cell culture systems. In the present study, we demonstrated for the first time that PIC profoundly

Fig. 5. Colonic mRNA expression of inflammatory mediators in dextran sulfate sodium (DSS)-exposed, piceatannol (PIC)-treated mice. Colon tissue from DSS-exposed, PIC-treated mice and from DSS-treated control mice were prepared on day 10 after DSS exposure, and real-time RT-PCR was performed as described in the Materials and methods section. Values are means ± SEM. Significant differences in the DSS group, *P < 0.05, **P < 0.01 and ***P < 0.001.
attenuates DSS-induced colitis in mice; this likely occurred through attenuation of NF-κB and STAT-3 activation. Another important observation is that oral administration of PIC significantly ameliorated colitis, as shown by suppression of colon shortening and pro-inflammatory cytokine and chemokine production. PIC was able to attenuate clinical symptoms of colitis in the present study, even at low dose (2.5 mg/kg). Since 1 mg/kg PIC treatment could not reverse general symptoms of colitis, the effective minimum dose of PIC might be 2.5 mg/kg.

NF-κB is the key transcription factor for inflammatory responses, and it is thought to be important in activation and progression in both humans with IBD and in animal models of colitis [31,32]. Indeed, disease activity in mice with colitis is inhibited by antisense oligonucleotides that inhibit the p65 subunit of NF-κB, which suggests a critical role for NF-κB in mediating the inflammatory response [32]. Attempts to control mucosal inflammation through the use of agents that block the NF-κB pathway have met with some success in murine models. For example, it has been shown that NF-κB decay ameliorates disease severity in several murine experimental colitis models. The mechanism by which PIC inhibits inflammatory cytokine (IL-1β, IL-6, and TNF-α) and chemokine (MCP-1 and KC) production seems to be through the downregulation of NF-κB-mediated activation, since p65 in the nuclear fraction of DSS-treated mice was significantly decreased when they were pretreated with PIC. NF-κB activation is believed to play a major role in the regulation of pro-inflammatory gene transcription, and its suppression by PIC may inhibit early steps in inflammation and modulate upregulation of multiple pro-inflammatory genes. Binding sites for the NF-κB family of transcription factors are found in the promoter and enhancer regions of a multitude of genes, including those corresponding to cytokines, chemokines, and growth factors that are known to be involved in the inflammatory response.

In addition, it has been shown that cytokines exert their biological functions through JAK and STAT transcription factors. An experiment blocking the IL-6 receptor has demonstrated that IL-6 plays an important role in the development of colitis by activating the STAT3 signaling pathway [33]. Indeed, STAT3 is most strongly tyrosine-phosphorylated in human UC and CD patients and in mice with DSS-induced colitis [12]. These results suggest that the IL-6/STAT3 pathway plays a crucial role in the development and perpetuation of DSS-induced colitis, and an agent capable of modulating STAT3 activity could control intestinal inflammation. The expression of phosphorylated colonic STAT-3 was drastically reduced in PIC-treated mice exposed to DSS, compared to mice that were exposed to DSS, but not treated with PIC (Fig. 3).

IBD is an immunologically-mediated collection of disorders. The etiology of IBD remains largely unknown. However, both genetic and environmental factors seem to contribute to the pathogenesis of the disease. Present treatment for colitis includes nonsteroidal anti-inflammatory drugs, corticosteroids, and immunosuppressants such as azathioprine and methotrexate. Unfortunately, adverse effects limit their use, especially when given long-term. A humanized anti-TNF-α is also being applied clinically. However, antibody treatment may also have serious side effects [34]. To our knowledge, the only stilbenes that have been previously shown to reverse experimental colitis are resveratrol in trinitrobenzenesulfonic acid-induced colitis rats [35] and 2,3,5,4-tetrahydroxystilbene-2-O-beta-D-glucoside (THSG) in acetic acid-induced colitis mice [36]. Administration of 10 mg/kg resveratrol significantly attenuated the damage score and corrected the disturbances in morphology associated to injury via the reduction of NF-κB protein expression [35]. In addition, over the 60 mg/kg of TSHG treatment ameliorated colon damage, inhibited the increased of acetic acid-induced MPO activity and NO levels [36]. Since low dose of PIC (2.5 mg/kg) inhibited loss of body weights, shortening of colon length, disruption of the colonic architecture, a significant reduction in colonic MPO activity, and a decrease in pro-inflammatory cytokines mRNA levels, PIC might be an effective stilbene for the treatment of colonic inflammation.

Acknowledgement

This work was supported by the Korea Science and Engineering Foundation (KOSEF) grant funded by the Korea government (MOST) (R01-2007-000-20164).

References


