Allicin inhibits spontaneous and TNF-\(\alpha\) induced secretion of proinflammatory cytokines and chemokines from intestinal epithelial cells

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Received 26 June 2003; accepted 31 March 2004

Summary Background & aims: Allicin, the active substance of fresh crushed garlic has different biological activities and was implicated as an anti-inflammatory agent. Epithelial cells have an important role in intestinal inflammation. The aim of this study was to assess the immunomodulatory effect of allicin on intestinal epithelial cells.

Methods: The spontaneous and TNF-\(\alpha\)-stimulated secretion of IL-1\(\beta\), IL-8, IP-10 and MIG from HT-29 and Caco-2 cells was tested with, or without pretreatment with allicin. Cytokine secretion was assessed using ELISA and expression of mRNA was determined by an RNA protection assay.

Results: Allicin markedly inhibited the spontaneous and TNF-\(\alpha\) -induced secretion of IL-1\(\beta\), IL-8, IP-10 and MIG from the two different cell lines in a dose-dependent manner and suppressed the expression of IL-8 and IL-1\(\beta\) mRNA levels. In addition, allicin suppressed the degradation of I\(\kappa\)B. No effect on cell viability was noted.

Conclusions: These observations indicate that allicin exerts an inhibitory immunomodulatory effect on intestinal epithelial cells and suggest that allicin may have the potential to attenuate intestinal inflammation.

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Introduction

Intestinal epithelial cells form the first line of defense against the luminal microbial flora and directly contact and absorb intraluminal nutrients.
The protective function of the intestinal mucosa is achieved both by forming a physical barrier, as well as by elicitation of a controlled immune response which is mediated by secretion of proinflammatory cytokines and chemokines. Proinflammatory cytokines such as TNF-α and IL-1β are involved in a variety of biological processes including cell activation and differentiation and therefore, have a major role in the inflammatory process. Chemo- kines such as IL-8, MIG (monokine induced by INF-γ) and IP-10 (INF-γ-inducible protein of 10 kD) mediate the inflammatory response by recruitment of various circulating leukocytes into the inflamed tissue. While secretion of proinflammatory cytokines and chemokines may be protective, overproduction of these mediators may be detrimental. Such uncontrolled inflammatory response is hypothesized to be significant in the pathogenesis of inflammatory bowel disease.

The close physical interaction between the gut mucosa and luminal nutrients may affect biological processes within the intestinal epithelial cells. Intraluminal food was shown to be crucial for keeping the integrity of the gut mucosa. Moreover, nutrients are able to affect both the systemic and mucosal immune response and micronutrients such as trace elements and vitamins have been shown to affect the mucosal cytokine profile.

The safety of such treatments as compared to the toxicity of the current immunosuppressive agents merits further research into the mechanisms by which food ingredients can affect the inflammatory process within the intestinal mucosa.

Throughout the history, garlic was considered as a healing agent by many different cultures. It is still used in complementary and alternative medicine for a wide variety of illnesses. Allicin is the active substance of fresh crushed garlic and is also responsible for the special strong odor of crushed garlic. Recently, allicin was reported to affect different biological activities such as antibacterial, antiparasite and antifungal activities. It was also shown that garlic preparations may reduce serum lipid levels, as well as inhibit platelet aggregation. Interestingly, allicin has radical-scavenging properties in activated granulocytes and may also inhibit inducible nitric oxide synthase expression in activated macrophages. These properties may affect the immune function of epithelial cells as well. Due to the potential for close contact between allicin and intestinal epithelial cells and the biological effects of allicin, the aim of this study was to determine whether allicin exerts an immune modulatory effect on intestinal epithelial cells.

**Methods**

**Reagents**

TNF-α was obtained from Boehringer Mannheim (Indianapolis, USA). Allicin was kindly donated by Prof. D. Mirelman (The Weizmann Institute of Science, Rehovot, Israel). Allicin in pure form (2 mg/ml in phosphate buffer 50 mM, pH 6.5) was prepared by reacting a solution of the synthetic substrate, alliin with a stabilized preparation of garlic alliinase as previously described. The purity and concentration of the allicin solutions was routinely determined by using high-performance liquid chromatography (HPLC).

**Cell lines and culture**

HT-29 (ATCC HTB38) and Caco-2 (ATCC HTB27) cells were obtained from the American Type Tissue Culture Collection (Rockville, MD). The cells were maintained in culture (at 37°C, 5% CO2 incubation) in DMEM media (Bet-Haemek, Israel) supplemented with 10% Fetal calf serum (Bet-Haemek), 1% glutamine and 1% penicillin and streptomycin (Bet Haemek). Caco-2 cells were also supplemented with Neut-mix F12 (Life Technologies, Wien, Austria). Routine testing of cultures for Mycoplasma infection was negative. All incubations were carried out at 37°C.

**TNF-α and INF-γ-induced cytokine secretion**

HT-29 test cells were grown as confluent monolayers in 24-well tissue culture plates. After the cells reached confluence, the culture medium was replaced by fresh medium, and supplemented with allicin. After 30 min incubation, TNF-α was added at a concentration of 200 ng/ml, and the cells were returned to the incubator for 24-h. The cells were then harvested, the supernatants collected and the
concentrations of IL-1β, IP-10, MIG and IL-8 determined by ELISA.

For RNA extraction, cells were grown in 10 cm tissue culture dishes until they reached confluence. The medium was then replaced by fresh medium and supplemented with allicin and TNF-α as previously described. After 2 h of incubation, the cells were harvested and their RNA was extracted.

**Determination of cytokine secretion and cell viability**

IL-8 was measured by ELISA as described. Briefly, 96-well plates were coated with polyclonal goat anti-human IL-8 antibodies (R&D Systems, Minneapolis, MN), as capturing antibodies. After having been incubated with the tested supernatants and washed, polyclonal rabbit anti-human IL-8 detecting antibodies (Endogen, Boston, MA) were added. Alkaline phosphatase-labeled mouse anti-rabbit IgG (Sigma) was used as a second antibody. Quantification of bound antibodies was carried out using p-nitrophenylphosphate (Sigma). ELISA for IP-10 and MIG was performed as described. Briefly, 96-well plates were coated with monoclonal anti-human IP-10 or anti-human MIG antibodies (R&D Systems), as capturing antibodies. Biotinylated goat anti-IP-10 or anti-MIG (R&D Systems) were used as detection antibodies. Second-step reagents were horseradish peroxidase (HRP) conjugated to streptavidin. Bound HRP was visualized with TMB (Sigma Chemical Co., St. Louis, MO). Chemokine concentrations were calculated from standard curves using recombinant human IP-10 or MIG (R&D Systems). Three replicate samples were included in each experiment. Cell viability was determined using the MTT method, cell counting was performed in parallel to the MTT assay. Cell death was evaluated by detection of LDH in the supernatants using the CytoTox non-radioactive cytotoxicity assay (Promega, Madison, WI) according to the manufacturer's instructions.

**Western blot analysis**

HT29 cells cultured for 3 days were washed twice with phosphate buffered saline (PBS) and total protein was extracted. Protein determination was preformed by using the Bicinchoninic acid method (Pierce Biotechnology, Rockford, IL). Protein samples, 30 μg/lane, were size-separated using a standard 11% SDS polyacrylamide gel. After electrophoresis, proteins were transferred onto nitrocellulose filters (Schleicher and Schuell, Keene, NH) using a transblot apparatus in a buffer containing 192 mM glycine, 25 mM Tris, 0.025% SDS and 20% methanol. The filter was stained with 0.1% ponceau (Sigma) to assure equal loading and transfer. The filter was blocked by 5% non-fat milk in PBS containing 0.1% Tween 20 (TBS-T), for 1 h at room temperature and then incubated for 1 h at room temperature with rabbit anti-human hK-B-α (sc-203, Santa Cruz, Biotechnology Santa Cruz, CA) diluted 1:200 in 5% non-fat milk. The filter was washed three times with TBS-T and then incubated with a goat anti-rabbit antibody conjugated with horse-radish peroxidase (Zymed Laboratories, CA) at a dilution of 1:5000 at room temperature. The filter
was washed three times in TBS-T and developed using the ECL Western blot detection system kit (Pierce, Rockford, IL) according to the manufacturer’s recommended protocol.

Statistical analysis

All statistical analysis was performed using an unpaired, two tailed, t-test. P values greater than 0.05 were considered to be not significant. Error bars represent the variation between different experiments.

Results

Allicin inhibits the spontaneous and the TNF-\(\alpha\) induced secretion of IL-1\(\beta\) from two different cell lines

Intestinal epithelial cell lines such as HT-29 are known to spontaneously secret IL-1\(\beta\).\(^{27}\) IL-1\(\beta\) is a major pro-inflammatory cytokine and the ratio between IL-1\(\beta\) and IL-1 receptor antagonist (RA) seems to be important in active inflammatory bowel disease.\(^{30,31}\) TNF-\(\alpha\) is an important proinflammatory cytokine as well and previous studies pointed to its important role in mucosal inflammation.\(^{5,32,33}\) Therefore, the effect of allicin on spontaneous and TNF-\(\alpha\)-stimulated secretion of IL-1\(\beta\) was studied. As shown in Fig. 1A, allicin inhibited the spontaneous secretion of IL-1\(\beta\) from HT-29 cells in a dose-dependent manner, from a baseline of 0.1 ± 0.02 pg/ml. The slight increase in IL-1\(\beta\) concentration noted at 5 \(\mu\)M, was not statistically different compared to the control. The initial effect of allicin was apparent at a concentration of 20 \(\mu\)M. TNF-\(\alpha\) stimulated the secretion of IL-1\(\beta\) from 0.06 to 2.5 pg/ml (data not shown). As shown in Fig. 1B, allicin inhibited the stimulated secretion of IL-1\(\beta\) as well, in dose-dependent manner, starting at 20 \(\mu\)M and reaching 57% inhibition at a concentration of 40 \(\mu\)M.

To test whether the inhibitory effect of allicin was restricted to one cell line only, or whether it represented a more general phenomenon, allicin was applied to Caco-2 cells and its effect on cytokine secretion was tested. As illustrated in Fig. 1C and D, allicin had a similar effect on Caco-2 cells. Both the spontaneous and TNF-\(\alpha\) -induced secretion of IL-1\(\beta\), was inhibited in a dose-dependent manner. The inhibitory effect was initiated at a concentration of 20 \(\mu\)M. The slight increase in IL-1\(\beta\) concentration noted at 10 \(\mu\)M, was not statistically different relative to the control.

To rule out the possibility that the inhibitory effect of allicin resulted from inhibition of cell proliferation or cytotoxicity, MTT and LDH cytotoxicity assays were performed following incubation of 30,000 cells with allicin. As shown in Table 1, no effect on cell viability or proliferation was noted, indicating that the effect of allicin was mediated by its intracellular effects. Changes in the MTT assay may reflect not only cell death, but also variation in cell number. Therefore, the release of lactate dehydrogenase from cells to the medium was measured as another marker for cell viability, which is less influenced by cellular proliferation. As shown in Table 2, the results of

![Figure 1](image-url)  
**Figure 1**  
HT-29 cells (A & B) and Caco-2 cells (C & D) were grown until confluence and incubated in the presence of allicin overnight. Supernatants were collected and assayed by ELISA for the concentration of IL-1\(\beta\). In panels B and D, allicin was added for 1 h, after which TNF-\(\alpha\) (200 ng/ml) was added, and the cells were incubated for additional 20 h. The reduction in the concentration of IL-1\(\beta\) from baseline was significant at allicin concentration of 20 \(\mu\)M (\(P<0.0001\) for A and C, \(P<0.001\) for B and D). One experiment representative of three is shown. Error bars represents SD.
the LDH assay confirm the results of the MTT assay and show no effect of allicin on cell viability at the concentrations that affected cytokine secretion. Cell counting was performed in parallel to the MTT assay and revealed no difference between allicin-treated cells and the controls at a concentration of 80 \( \mu \text{M} \) of allicin (data not shown).

### Table 1: Viability of HT-29 or Caco-2 cells following treatment with allicin as assessed by the MTT assay.

<table>
<thead>
<tr>
<th>Allicin (( \mu \text{M} )) (%control)</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>80</th>
<th>100</th>
<th>150</th>
<th>200</th>
</tr>
</thead>
<tbody>
<tr>
<td>HT 29</td>
<td>95±7</td>
<td>93±4</td>
<td>97±5</td>
<td>94±8</td>
<td>93±6</td>
<td>84±8</td>
<td>58±5</td>
</tr>
<tr>
<td>Caco-2</td>
<td>98±7</td>
<td>95±8</td>
<td>94±7</td>
<td>98±8</td>
<td>94±7</td>
<td>72±9</td>
<td>61±7</td>
</tr>
</tbody>
</table>

HT-29 or Caco-2 cells were grown to confluence in 96-well plates (30,000 cells per well). Following culture, the cells were incubated with allicin overnight at 37°C. Subsequently, an MTT assay was performed, and the results were quantified by measurement of \( \text{OD}_{570} \) and presented as percent of control (non-treated cells). The results represent the mean±SD of two different experiments, each performed in triplicate.

### Table 2: Allicin does not affect the viability of HT-29 or Caco-2 cells following treatment with allicin as assessed by the LDH cytotoxicity assay.

<table>
<thead>
<tr>
<th>Allicin (( \mu \text{M} ))</th>
<th>0</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>15</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>HT-29 (OD)</td>
<td>0.266±0.04</td>
<td>0.263±0.03</td>
<td>0.268±0.06</td>
<td>0.270±0.04</td>
<td>0.270±0.04</td>
<td>0.270±0.04</td>
<td></td>
</tr>
<tr>
<td>Caco-2 (OD)</td>
<td>0.270±0.03</td>
<td>0.266±0.05</td>
<td>0.266±0.04</td>
<td>0.273±0.04</td>
<td>0.265±0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HT-29 or Caco-2 cells were grown to confluence in 96-well plates (30,000 cells per well). Following culture, the cells were incubated with allicin overnight at 37°C. Subsequently, an LDH cytotoxicity assay was performed, and the results were quantified by measurement of \( \text{OD}_{490} \) readings. The results represent the mean±SD of two different experiments, each performed in triplicate.

Allicin inhibits the spontaneous and the TNF-\( \alpha \)-induced secretion of IL-8 from two different intestinal cell lines

The chemokine IL-8 has a central role in attracting neutrophils to the inflamed mucosa. Therefore, we tested whether the effect of allicin was restricted to the secretion of proinflammatory cytokines, or whether it affected the secretion of the chemokine IL-8 from HT-29 cells. These cells were shown to secrete IL-8 spontaneously.\(^{27}\) As shown in Fig. 2A, allicin inhibited the secretion of IL-8 in a dose-dependent manner from a baseline of 25±9.6 pg/ml reaching more than 50% inhibition at a concentration of 20 \( \mu \text{M} \). Furthermore, allicin also inhibited the TNF-\( \alpha \)-induced secretion of IL-8 and reached more than 50% inhibition at a concentration of 40 \( \mu \text{M} \) and over 90% inhibition at a concentration of 80 \( \mu \text{M} \) (Fig. 2B). Similar findings were observed using Caco-2 cells (Fig. 2C and D). We next tested whether allicin affects the cells only when applied prior to the proinflammatory stimulation, or whether it is effective when it is applied in parallel as well. Cells were treated with TNF-\( \alpha \), following either preincubation, or coincubation with allicin. As shown in Fig. 2E, preincubation with allicin produced more than 50% inhibition. However, cotreatment with allicin and TNF-\( \alpha \) was inhibitory as well and resulted in inhibition of the TNF-\( \alpha \)-induced secretion of IL-8 by 30%. Allicin inhibits the secretion of IP-10 and MIG from intestinal cell lines

Whereas neutrophils are dominant mainly in the acute inflammatory response, T-lymphocytes play a role in many chronic intestinal inflammatory processes such as Crohn’s disease. Therefore, we investigated the effect of allicin on the secretion of lymphocyte-specific chemokines such as IP-10 and MIG. TNF-\( \alpha \) potentiates the secretion of IP-10 and MIG from epithelial cell lines following stimulation by INF-\( \gamma \).\(^{34}\) The combination of both cytokines was used to induce a maximal proinflammatory response. As shown in Fig. 3A and B, allicin suppressed both the spontaneous and induced secretion of IP-10. To further extend this observation, the effect of allicin on the secretion of MIG was tested as well. As shown in Fig. 4, allicin markedly inhibited the secretion of MIG. Notably, this inhibition occurred at a relatively low concentration of allicin (5 \( \mu \text{M} \)) in both non-stimulated Caco-2 cells (Fig. 4A) and cells that were treated with INF-\( \gamma \) and TNF-\( \alpha \) (Fig. 4B). Similar results were obtained with HT-29 cells (data not shown).
Allicin suppresses IL-1β and IL-8 mRNA steady state levels

The inhibition of cytokine secretion may occur at a number of sub-cellular levels, such as transcription or translation. To test whether allicin regulated mRNA levels, we determined the relative levels of IL-1β and IL-8 mRNA using an RNA protection assay (RPA). HT-29 cells were grown to confluence and preexposed to allicin, after which the cells were stimulated by TNF-α. After 2 h of incubation with TNF-α, RNA was extracted and its levels were assessed by an RPA. The 2-h time point was chosen because the up-regulation of the IL-8 mRNA concentration after stimulation by TNF-α was shown to be maximal at this time.35 As shown in
Fig. 5A and B, allicin markedly suppressed the steady state mRNA levels of IL-1β and IL-8 following stimulation with TNF-α.

Allicin inhibits the degradation of IκBα degradation

The NFκB pathway is has a central role in regulation of transcription of proinflammatory mediators like cytokines and chemokines. A critical step in the regulation of NFκB activity is the degradation of IκB which follows its phosphorylation by IκB kinases (IKK). Thus, degradation of IκB is an indirect marker for the activation of NFκB. To test the effect of allicin on the activation of NFκB, we performed a Western blot analysis in which IκBα was detected following treatment with TNF-α. As shown in Fig. 6, TNF-α induced a rapid degradation of the IκBα protein and lead to its complete disappearance by 10 min (Fig. 6, lane 3). This was followed by a re-appearance, that started 30 min after stimulation with TNF-α (lane 5). Pre-incubation of the cells with allicin resulted in inhibition of IκBα degradation (lanes 3–5 (no allicin) as compared to lanes 6–8 (with allicin).
These results suggest that allicin exerted its effects on cytokine transcription, at least in part via its effects on the NFκB signal transduction pathway.

Discussion

In this study we show for the first time that allicin, a bioactive component of garlic, has potent anti-inflammatory effects on intestinal epithelial cells. Our observations indicate that allicin suppresses both the spontaneous and TNF-α-stimulated secretion of the chemokines IL-8, MIG and IP-10, as well as the secretion of IL-1β from intestinal epithelial cells. Furthermore, we show that this effect was mediated at least in part by down regulation of mRNA levels and involved inhibition of activation of the NFκB pathway.

Even though garlic (Allium sativum) was used for centuries as a prophylactic and therapeutic medicinal agent, the exact mechanism that underlies its biological activity is still not fully understood. Whole garlic typically contains about 1% allein, which is the odorless precursor of allicin. Alli-nase, which is an enzyme that is located within a separate compartment in natural garlic, converts allein into the biologically active allicin following the crushing of garlic and the contact between the enzyme and the substrate. Of note, in higher doses ( > 100 μM) allicin may be toxic to mammalian cells as well. Theoretically, this cytotoxic effect could have been the cause for reduced expression of epithelial chemokines and cytokines. Therefore, cell viability and potential cytotoxicity were determined after treatment of the cells with allicin using both the MTT assay and release of LDH. Consistent with the results obtained by others, both assays detected a cytotoxic effect only in concentrations above 100 μM, thus indicating that cell death was not the mechanism by which allicin exerted its effects on the epithelial cells. Moreover, the RPA demonstrated that allicin inhibited the expression only of IL-1β and IL-8 mRNA and not that of the housekeeping gene GAPDH. This finding further demonstrated that the effect of allicin was not mediated by cellular death but rather by specific inhibition of expression and secretion of the proinflammatory molecules.

The current study demonstrated that allicin inhibited the degradation of IkBa. The NFκB heterodimer is retained in the cytoplasm in an inactive form through association with one of the IkB inhibitory proteins. Following stimulation by proinflammatory mediators such as TNF-α and IL-1β, IkB is phosphorylated by a specific kinase complex (IKK) which leads to its ubiquitination, and subsequent proteolysis by the 28s proteosome. The degradation of IkB releases active NFκB which translocates to the nucleus and regulates gene expression by binding to κB binding sites or by interacting with other transcription factors. Many cellular genes that are involved in the inflammatory response are regulated by the NFκB pathway. Thus, inhibition of the NFκB pathway by allicin would predictably reduce the elaboration of NFκB-mediated cytokine secretion. This observation is consistent with the finding of reduced levels of IL-1β and IL-8 mRNA and provides a potential mechanism by which allicin may regulate transcription. Notably, a previous study that investigated the effect of allicin on cardiac myocytes demonstrated that it inhibited the activity of inducible nitric oxide synthase and the CAT-2 arginine transporter. By doing so, it had the potential to attenuate the effect of proinflammatory cytokines on the production of nitric oxide. Since nitric oxide synthase and nitric oxide are expressed in epithelial cells, it might be speculated that inhibition of the nitric oxide system by allicin may be an additional mechanism by which its effect was mediated.

The effect of allicin was dose-dependent and occurred at concentrations as low as 5–20 μg/ml. Allicin has a short half-life and it is disintegrated to other compounds such as diallyl sulfide, disulfides, trisulfides and ajoene. Allicin can not be detected in the blood or urine after ingestion of raw garlic or pure allicin. This suggests that it cannot act through the blood stream following oral ingestion. However, in the current study we have shown that allicin directly affected the intestinal epithelial cells suggesting that luminal allicin may affect the intestinal mucosa by direct contact, independently of its circulating levels.

The direct effect of allicin on intestinal epithelial cells may be of particular importance in inflammatory bowel diseases. A number of cell populations play a role in the pathogenesis of IBD including PMNs and lymphocytes. Indeed, elevated concentrations of PMN-specific chemokines such as IL-8 were detected in tissues of IBD patients. Secretion of Th1-type cytokines is thought to play an important role in the pathogenesis of Crohn’s disease. Previous studies have shown that CD4 lymphocytes that secrete Th1-type cytokines can be selectively recruited by the chemokines IP-10, MIG and IFN-inducible T-cell a chemotactant (I-TAC). The secretion of these chemokines can be triggered by INF-γ. Recently, Dwinell et al, have shown that intestinal epithelial cells constitutently express IP-10 and MIG and that this
expression is enhanced by INF-γ and may be even further potentiated by TNF-α. Of relevance, Shibahara et al, reported that intra-epithelial lymphocytes (IELs) express the chemokine receptor CXR3 and thus, IP-10 and MIG may serve as chemotactants for IEL. IL-1β is another important mediator of mucosal inflammation. Previous studies have shown that the ratio between the pro-inflammatory IL-1β and the anti-inflammatory molecule IL-1 RA is altered in inflammatory bowel disease toward increased levels of IL-1 and decreased IL-1RA concentrations. Herein, we demonstrated that allicin significantly inhibited the secretion of IL-8, IP-10, MIG and IL-1β from intestinal epithelial cells. This observation suggests that local application of allicin may serve as a potential immune-mediating therapy in inflammatory bowel diseases.

Our studies were performed using two adenocarcinomas-derived cell lines. Previous studies have shown that these two cell lines respond to TNF-α stimulation in a manner similar to freshly isolated intestinal epithelial cells and express a similar array of chemokine receptors. These similarities suggest that our findings with the HT-29 and Caco-2 cells represent immune regulatory mechanisms that may be of relevance to normal epithelial cells as well.

It should be noted that garlic preparations might also have some harming effects on the gastrointestinal mucosa. Consumption of large amounts of garlic may cause a burning sensation and diarrhea. Moreover, different preparations of garlic were tested using a dog model, and were shown to cause redness and erosions of the gastric mucosa following direct application to the stomach, and some loss of epithelial cells when delivered as enteric-coated products. Other preparations such as AGE were reported to protect the mucosa following direct application to the stomach. It is not clear yet what component of garlic is responsible for the potential damaging effect, but clearly, pure allicin should be evaluated to exclude a damaging effect on the gut mucosa in an in vivo model prior to its administration as a therapeutic agent.

In conclusion, the present study shows that allicin, the main biologically active substance of freshly crushed garlic, modulates cytokine and chemokine secretion from intestinal epithelial cell lines. These observations suggest that allicin should be tested in in vivo models to evaluate its therapeutic potential in intestinal inflammatory diseases.

References


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