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Original Research Article

Anti-inflammatory Effects of *Allium victorialis* Extract in Lipopolysaccharide Exposed Rats and Raw 264.7 Cells

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Abstract - This study examined the inflammatory reaction effects of *Allium victorialis* var. *platyphyllum in vivo* at the time of a lipopolysaccharide (LPS) shock in rats, and *in vitro* in cultured Raw 264.7 cells, with the aim of facilitating the development of a new anti-inflammatory medicine. Plasma concentrations of interleukin (IL)-1β, IL-6, tumor necrosis factor α (TNF-α), and IL-10 in rats peaked 5 h after LPS treatment in all experimental groups, with those of IL-1β, IL-6, and TNF-α being significantly lower in all animals treated with *A. victorialis* than in the control group at that time point. Conversely, the plasma concentration of IL-10 was higher in the rats treated with 300 ㎎/㎏ *A. victorialis* extract than in the control group at both 2 and 5 h after LPS treatment. Concentrations of IL-1β and IL-6 in the liver of rats treated with *A. victorialis* extract were significantly lower than those of the saline-treated control group. However, the liver concentrations of TNF-α and IL-10 did not vary significantly between the four animal groups. Similarly, concentrations of IL-1β, IL-6, and TNF-α obtained from cultured Raw 264.7 macrophages were lower in all of the *A.-victorialis*-extract-treated groups than in the control group. Although the concentration of IL-10 in the *A.-victorialis*-extract-treated groups tended to be greater than in the control group, the differences between groups were not statistically significant. Together the findings of this study suggest that *A. victorialis* var. *platyphyllum* contains functional substances that are involved in inflammatory reactions.

Key words - *Allium victorialis* extract, Lipopolysaccharide, Anti-inflammatory, Cytokine

Introduction

Numerous recent studies have investigated the development of new anti-inflammatory substances that will effectively resolve inflammatory reactions without inducing side effects. Testing of various oriental medicinal herbs and natural resources that have proved effective in private therapies and oriental medicine have yielded good results, stimulating interest in functional natural substances (Lee, 2007).

Allium victorialis var. *platyphyllum*, a medicinal herb that has been traditionally widely used to treat various conditions such as hypertension, arteriosclerosis, gastritis, and stomachache (Kim *et al*., 2010), is reported to contain bioactive substances such as astragalin, kaempferol, allicin, ferulic acid, methylallyldisulfide, diallydisulfide, quercetin, and furostanol glycosides (Lee *et al*., 2007). Bioactivity experiments have demonstrated that the plant is effective in lowering lipids and obesity, resisting oxidation, diabetes, and cancer, and protecting the liver (Kim *et al*., 2000; Lee *et al*., 2001; Shirataki *et al*., 2001; Ham *et al*., 2004; Lee *et al*., 2004; Choi *et al*., 2005). A review of research findings on traditional therapies and natural substances with bioactive functions suggests that *A. victorialis* var. *platyphyllum* could contain substances that are reactive to inflammation. Further study into the behaviors of this organism and its physiological effects are thus warranted.

An endotoxin of pathogenic bacteria, lipopolysaccharide (LPS), facilitates the production of cytokines that stimulate the activities of various kinds of inflammatory cells and other tissues (Marriot *et al*., 1998). Macrophages such as Raw 264.7 cells or monocytes increase the production of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and interleukin-1β (IL-1β) (Binetruy *et al*., 1991; Funk *et al*., 1991; Willeaume *et al*., 1996; Bhattacharyya *et al*., 2002), they are generally applied as an experimental model for studying inflammatory reactions *in vitro* (Mathiak *et al*., 2000). Therefore, this study examined the inflammatory reaction effects of *Allium victorialis* var. *platyphyllum* in vivo at the time of a lipopolysaccharide (LPS) shock in rats, and *in vitro*

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in cultured Raw 264.7 cells, with the aim of facilitating the development of a new anti-inflammatory medicine.

Materials and Methods

Preparation of *A. victorialis* extract

The leaf portion of air-dried *A. victorialis* var. *platyphyllum* MAKINO (Yecheon product, April harvest, 500 g dried weight) was separated from the rest of the plant and extracted three times for 5 h each in a cooling water reflux cistern, decompression concentrated, and then extracted using ethanol yield, 121 g and stored under refrigeration at 2℃.

Animal treatments and LPS injection

Twenty-four male Sprague-Dawley rats (Orient Bio co., body weight: 213.27 ± 5.11 g, mean ± SD) were adapted to a basal diet (Table 1) for 1 week and then divided randomly into four groups (n = 6 animals per group) according to the planned treatment as follows: (1) control group (normal saline, 100 ㎎/㎏/day), (2) *A. victorialis* var. *platyphyllum* extract (hereafter referred to as *A. victorialis* extract) at 100 ㎎/㎏/day, (3) *A. victorialis* extract at 200 ㎎/㎏/day, and (4) *A. victorialis* extract at 300 ㎎/㎏/day. The saline and various concentrations of *A. victorialis* extract were administered orally via a Jones tube at 5 p.m. each day for 6 weeks. Water and a standard diet were provided to all animals *ad libitum* throughout the experiments. At the end of the 6-week treatment period, all animals were administered an intra-abdominal injection of LPS (5 ㎎/㎏). Blood was drawn from all of the animals at the end of the 6-week treatment period at three time points: 0, 2, and 5 h after LPS injection. The blood was sampled via cardiac puncture under ether anesthesia. The livers of all animals were harvested through a midabdominal incision after the final blood sample was taken.

Table 1. Composition of experimental diet

Ingredients (%)	Basal diet
Casein	20.0
α-Corn starch	35.5
Sucrose	11.0
Lard	4.0
Corn oil	1.0
Mineral mix[z]	3.5
Vitamin mix[y]	1.0
Cellurose powder	23.7
DL-methione	0.3

[z]Mineral mix. (g/㎏ diet) : $CaCO_3$, 29.29; $CaHPO_4 \cdot 2H_2O$, 0.43; KH_2PO_4, 34.30; NaCl, 25.06; $MgSO_4 \cdot 7H_2O$, 9.98; Feric citrate hexahydrate, 0.623; $CuSO_4 \cdot 5H_2O$, 0.516; $MnSO_4 \cdot H_2O$, 0.121; $ZnCl_2$, 0.02; KI, 0.005; $(NH_4)_6$ $MO_7O_{24} \cdot 4H_2O$, 0.0025.

[y]Vitamin mix (㎎/㎏ diet) : Thiamine-HCl, 12; Riboflavin, 40; Pyrodoxin-HCl, 8; Vitamin-B_{12}, 0.005; Ascorbic acid, 300; D-biotin, 0.2; Menadione, 52; Folic acid, 2; D-calcium pantothenate, 50; P-aminobenzoic acid, 50; Nicotinic acid, 60; Cholin choloride, 2000 (IU/㎏ diet); Rethinyl acetae, 5000 (IU/㎏ diet); Cholecalciferol, 250 (IU/㎏ diet).

Raw 264.7 cell culture and treatment

Raw 264.7 cells were purchased from Korea Cell Bank (Seoul, Korea), and cultured in Dulbecco's modified Eagle's medium containing 10% fetal bovine serum, penicillin (100 U/㎖), and streptomycin (100 ㎍/㎖) in an incubator at 37℃ and under 5% CO_2. Cells from cultures that had reached 80~90% confluency and that had not exceeded 20 passages were used in the experiments. The cells were divided into four groups according to the planned treatment: (1) 0, (2) 10, (3) 30, and (4) 100 ㎍/㎖ divided *A. victorialis* extract. The cells were placed into wells at a concentration of 10^6/㎖ and incubated with *A. victorialis* extract as per their group assignment for 1 h, after which LPS was added to all groups at a concentration of 1 ㎍/㎖. Specimens were collected 6 h after this LPS shock.

Sample preparation and analysis

The blood samples were immediately centrifuged at 3000 rpm for 10 min, and the serum fractions were collected, frozen, and stored at −80℃ until required for analysis. Liver samples were prepared for analysis as follows: 1 g of liver particles was homogenized on ice in 5 ㎖ of cold phosphate-buffered saline (PBS, pH 7.4) containing a protease inhibitor cocktail (Table Complete Roche, Mannheim, Germany). The samples were centrifuged at 15,000 rpm for 15 min at 4℃. The supernatants were filtered through a 0.45-㎛ filter (Millex-HA, Millipore, Molsheim, France) and again centrifuged at 15,000 rpm for 15 min at 4℃. The resulting liver extracts were collected and stored at −80℃ until cytokine analysis was performed.

The Raw 264.7 cells were centrifuged at 15,000 rpm for 15 min at 4℃, and the resulting supernatants were filtered through a 0.45-㎛ filter (Millex-HA, Millipore) and stored under refrigeration at −80℃ until required for cytokine analysis.

The concentration of various cytokines (IL-1β, TNF-α, IL-6, and IL-10) in the prepared samples of plasma, liver, and Raw 264.7 cells were determined by enzyme-linked immunosorbent assay, using commercially available kits (Biosource International, Camarillo, CA, USA). The minimum detectable concentration of TNF-α was 0.7 pg/㎖, and those of the other cytokines were 3−8 pg/㎖. The concentration of hepatic cytokines was calculated per 1 g of wet tissue in 5 ㎖ of PBS. Plasma and Raw cell cytokine concentrations are expressed as pg/㎖, and hepatic cytokine concentrations as pg/㎎ of tissue.

Statistical analysis

The data were analyzed by one-way ANOVA by using an SPSS package, and the significance of differences between the groups was determined using Duncan's multiple-range test. The threshold for statistical significance was set at $P < 0.05$.

Results and Discussion

An acute inflammatory reaction was induced in this study by administering LPS to rats treated with *A. victorialis* extract at various concentrations, and the inflammatory cytokine contents of the blood and liver were measured over time. The effects of LPS shock on the cytokine activity of *A.-victorialis*-extract-treated Raw 264.7 cells were also measured.

Animal experiments

The levels of inflammatory cytokines in the blood will generally vary noticeably over time (Mathiak *et al*., 2000; Eduard *et al*., 2004), and so specimens were collected from the animals for plasma cytokine measurement prior to the LPS treatment (0 h), and 2 and 5 h thereafter. Liver specimens were collected at 5 h after LPS injection, at the end of the experiments. The LPS treatment concentration was set at 5 ㎎/㎏ based on the finding that this concentration has been shown to cause endotoxin shock in rats and mice over a short period of time, raising the cytokine concentrations in the liver and blood (Corral *et al*., 1996; Aono *et al*., 1997; Harry *et al*., 1999; Sang *et al*., 1999).

Plasma IL-1β

The results for plasma IL-1β concentration by treatment group over time after LPS treatment are shown in Fig. 1. The plasma concentration of IL-1β measured before LPS treatment (0 h) did not differ significantly between the four experimental groups. Concentrations increased rapidly at 2 h after LPS treatment in all treatment groups, but with no significant differences between them. A further, linear increase was observed at 5 h after LPS treatment. These findings concur with those reported by others, confirming that plasma IL-1β concentration reaches a peak at 4 h after LPS treatment (Mathiak *et al*., 2000; Eduard *et al*., 2004).

IL-1β and TNF-α share similar biological, proinflammatory functions, and are induce simultaneously to produce additive effects in response to acute inflammatory reactions. In this study, although levels of IL-1β were similar in the groups at 2 h after LPS, having increased rapidly, at 5 h the degree of further increment fell according to the concentration of *A. victorialis* extract with which the animals had been treated.

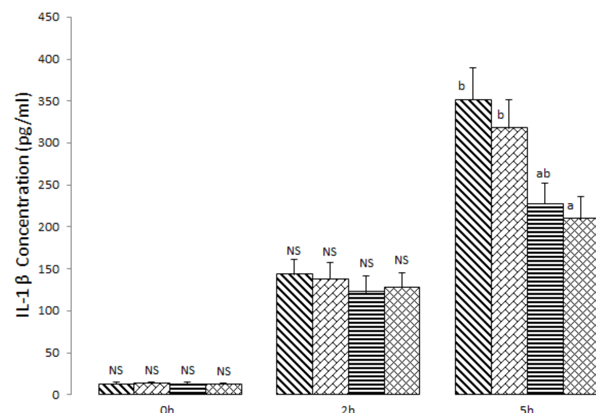

Fig. 1. Effects of *Allium victorial* extracts on IL-1β cytokines concentration.

[a,b]: Means in the same section with different superscripts are significantly different ($p < 0.05$).

[NS]: Not significantly different. 0, 2, 5 h : Blood collection time after LPS injection.

▧: Control, saline 100 ㎎/㎏; ▨: *Allium victorial* extracts 100 ㎎/㎏; ▤: *Allium victorial* extracts 200 ㎎/㎏; ▩: *Allium victorial* extracts 300 ㎎/㎏.

The plasma concentration of IL-1β was significantly lower in the 200 and 300 ㎎/㎏ treatment groups than in the control group. This result suggests that functional substances inherent in *A. victorialis* var. *platyphyllum* are involved in LPS-induced acute inflammatory reactions.

Plasma IL-6

Plasma IL-6 concentration increased rapidly at 2 h after LPS treatment in all treatment groups, continuing to increase thereafter until 5 h (Fig. 2). This finding is similar to previous reports (Mathiak *et al*., 2000; Eduard *et al*., 2004). As regards increments at particular time points, although plasma IL-6 concentrations in animals administered with *A. victorialis* extracts appeared to be lower than in the control group at 2 and 5 h after LPS treatment, only that of animals administered 300 ㎎/㎏ *A. victorialis* extract was significantly so. As with IL-1β, these findings suggest that functional substances inherent in *A. victorialis* var. *platyphyllum* are involved in LPS-induced acute inflammatory reactions.

Plasma TNF-α

TNF-α is an important mediator of the removal of endotoxins (Harbrecht *et al*., 1994) and is released by monocytes and macrophages. However, in the case of LPS shock, TNF-α causes liver-cell apoptosis (Chamulitrat *et al*., 1995), and thus excessive production of TNF-α can induce a large-scale pathogenic state. Accordingly, it is considered that regulation of TNF-α is a crucial task in inflammatory reactions (Hamada *et al*., 1999; Abul *et al*., 2007). In the present study, plasma TNF-α concentrations increased rapidly at 2 h of LPS treatment, with further increments leading to the level at 5 h being similar to that at 2 h (Fig. 3). However, as regards concentrations by treatment group, *A.-victorialis*-extract-treated groups exhibited lower values than in the control group, indicating that *A. victorialis* extract has a positive effect on TNF-α production.

Plasma IL-10

IL-10 suppresses synthesis of proinflammatory cytokines such as IL-6 and TNF-α, and has been shown to reduce T-cell revitalization in *in vitro* and *in vivo* (Clerici *et al*., 1994; Pender *et al*., 1999; Schotte *et al*., 2004). In the present experiments, plasma IL-10 concentration increased more in the groups treated with *A. victorialis* extract than in the control group both at 2 and 5 h after LPS treatment (Fig. 4). This suggests that IL-10 affected suppressed the production of this proinflammatory cytokine.

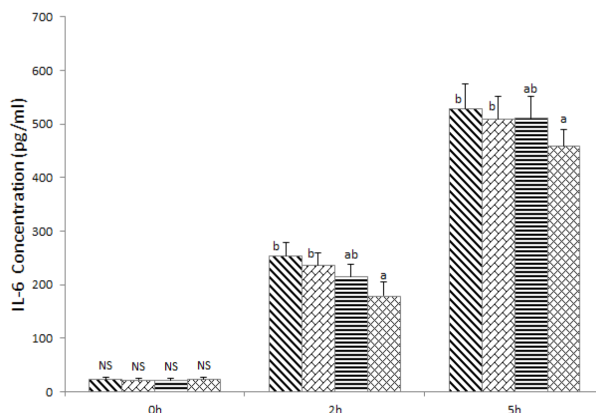

Fig. 2. Effects of *Allium victorial* extracts on IL-6 cytokines concentration.

a,b: Means in the same section with different superscripts are significantly different ($p < 0.05$).

NS: Not significantly different. 0, 2, 5 h : Blood collection time after LPS injection.

: Control, saline 100 ㎎/㎏; : *Allium victorial* extracts 100 ㎎/㎏; : *Allium victorial* extracts 200 ㎎/㎏; : *Allium victorial* extracts 300 ㎎/㎏.

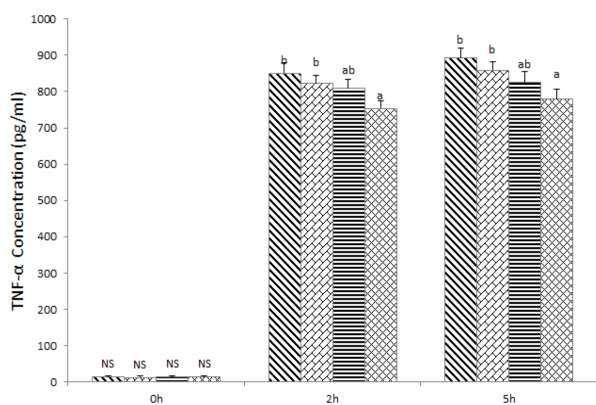

Fig. 3. Effects of *Allium victorial* extracts on TNF-α cytokines concentration .

a,b: Means in the same section with different superscripts are significantly different ($p < 0.05$).

NS: Not significantly different. 0, 2, 5 h : Blood collection time after LPS injection.

: Control, saline 100 ㎎/㎏; : *Allium victorial* extracts 100 ㎎/㎏; : *Allium victorial* extracts 200 ㎎/㎏; : *Allium victorial* extracts 300 ㎎/㎏.

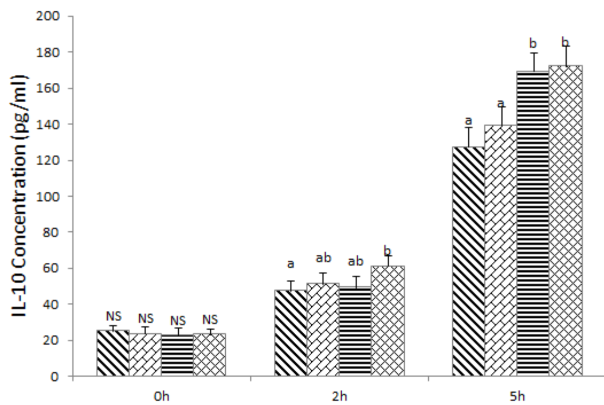

Fig. 4. Effects of *Allium victorial* extracts on IL-10 cytokines.

a,b: Means in the same section with different superscripts are significantly different ($p < 0.05$).

NS: Not significantly different. 0, 2, 5 h : Blood collection time after LPS injection.

▧: Control, saline 100 ㎎/kg; ▨: *Allium victorial* extracts 100 ㎎/kg; ▤: *Allium victorial* extracts 200 ㎎/kg; ▩: *Allium victorial* extracts 300 ㎎/kg.

Liver cytokines

The liver concentrations of cytokines are given in Table 2. The concentrations of IL-1β and IL-6 in the 300 ㎎/kg *A.-victorialis*-extract-treated group were significantly lower than in the control group, while the concentrations of TNF-α did not differ significantly between the four groups. As regards IL-10, although the *A.-victorialis*-extract-treated groups tended to exhibit higher concentrations than the control group, the differences were not statistically significant.

Together the findings of the *in vivo* experiments suggest that although *A. victorialis* extract does appear to affect LPS-shock-induced inflammatory reactions, the level of that effect may be substantially related with the degree to which cytokines synthesized in the liver are drained into the bloodstream. It has been reported that an LPS shock rapidly increases IL-1β concentrations within an interval as short as 30 min, with that increase being maintained for at least 3 h. (Mathiak *et al*., 2000; Eduard *et al*., 2004; Sang *et al*., 1999). Liver cytokines were thus measured at 5 h after LPS treatment, and the actual cytokine concentration is thought to have been measured during ongoing LPS shock.

Raw 264.7 cell culture experiments

The proinflammatory cytokines produced by *A.-victorialis*-extract-treated Raw 264.7 macrophage cells with LPS shock are listed in Table 3. IL-1β, IL-6, and TNF-α concentrations fell in all of the *A.-victorialis*-extract-treated groups compared with the control group. IL-10 concentrations tended to be somewhat higher in the former than the latter, but the differences did not reach statistical significance.

Table 2. Effects of *Allium victorials* extracts on liver cytokines concentration in lipopolysaccharide-exposed rats

Treatment	IL-1β (pg/㎎)	IL-6 (pg/㎎)	TNF-α (pg/㎎)	IL-10 (pg/㎎)
Control (saline, 100 ㎎/kg)	19.73 ± 3.97 bz	8.11 ± 1.92 b	1.91 ± 0.83 NSy	1.77 ± 0.54 NS
Allium victorials extracts (100 ㎎/kg)	20.11 ± 3.29 b	7.25 ± 1.55 ab	1.77 ± 0.61 NS	1.82 ± 0.51 NS
Allium victorials extracts (200 ㎎/kg)	14.53 ± 3.41 ab	6.33 ± 1.37 ab	1.62 ± 0.73 NS	1.83 ± 0.47 NS
Allium victorials extracts (300 ㎎/kg)	13.19 ± 3.51 a	5.91 ± 1.05 a	1.71 ± 0.75 NS	1.95 ± 0.64 NS

zMeans in the same column with different superscripts are significantly different ($p < 0.05$).
yNot significantly different.

Table 3. Effect of *Allium victorials* extracts on the concentration of inflammatory cytokines in lipopolysaccharide induced Raw 264.7 macrophages

Treatment	IL-1β (pg/㎖)	IL-6 (pg/㎖)	TNF-α (pg/㎖)	IL-10 (pg/㎖)
Control (0 ㎍/㎖)	28.11 ± 3.52 bz	16.39 ± 2.41 b	2.92 ± 0.61 b	2.11 ± 0.71 NSy
Allium victorials extracts (10 ㎍/㎖)	17.29 ± 3.14 a	10.11 ± 2.37 a	1.39 ± 0.59 a	2.53 ± 0.73 NS
Allium victorials extracts (30 ㎍/㎖)	16.73 ± 3.28 a	9.25 ± 1.83 a	1.27 ± 0.51 a	2.92 ± 0.77 NS
Allium victorials extracts (100 ㎍/㎖)	16.22 ± 3.16 a	8.84 ± 1.92 a	1.13 ± 0.43 a	2.97 ± 0.82 NS

zMeans in the same column with different superscripts are significantly different ($p < 0.05$).
yNot significantly different.

The variations in proinflammatory cytokines recorded *in vitro* were similar to those found for the *in vivo* experiments, suggesting that the *A. victorialis* extract could have been involved in the observed adjustment of the inflammatory reaction, and therefore that *A. victorialis* var. *platyphyllum* contains biologically functional substances that are involved in inflammatory reactions. Further study is warranted to examine in more detail the functional substances involved and their mode of action.

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