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Full Length Research Paper

Antimicrobial and immunomodulatory effects of *Aloe vera* peel extract

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The rapidly emerging rate of antibiotic resistance requires alternative solutions rather than new drugs. Aloe has been used for medical applications and exhibits antimicrobial activity as well as immunomodulation effects. Use of the aloe peel has not been considered, even though it may harbor many useful compounds. In this study, the antimicrobial activity of *Aloe vera* peel extract in distilled water against *Staphylococcus aureus*, *Bacillus* spp., *Enterococcus* spp., *Escherichia coli*, *Salmonella typhimurium, Pseudomonas aeruginosa*, and *Vibrio* spp. was ascertained. The number of bacterial colonies were significantly reduced by the application of peel extracts ($P<0.05$). The antimicrobial activity was especially strong against *E. coli* and *Vibrio* spp. ($P<0.001$). *In vivo* antimicrobial activity and immunomodulation effects were tested in mice challenged with *S. typhimurium* DT104. Fecal shedding *of S. typhimurium* DT104 significantly decreased and intestinal *Salmonella* specific IgA and IgG titers significantly increased in mice fed with peel extracts. In splenocyte cultures stimulated by concanavalin A, the extract did not affect the production of interleukin IL-2 and interferon-gamma but did promote the production of IL-4 and IL-10. The *in vitro* and *in vivo* antimicrobial activities and immunomodulatory properties of *A. vera* peel extract may be of commercial value.

Key words: *Aloe vera*, antimicrobial effect, immunomodulatory effect.

INTRODUCTION

Aloe vera, or *Aloe barbadensis* (Miller), has been widely used for the treatment of various ailments for millenia. The whole leaf of *A. vera* contains over 200 compounds including aloesin, anthraquinones (aloin and aloe-emodin), acemannan, saponins, sterols, amino acids and vitamins (Grindlay et al., 1986).

Most of the compounds have various biological activities with potential health benefits, such as anti-bacterial, antiviral, wound healing, antioxidant, immunomodulatory, antineoplastic, antihypertensive and antidiabetic activities (Chen et al., 2007; Gauntt et al., 2000; Grover et al., 2002; Im et al., 2005; Ozsoy et al., 2009; Pandey et al., 2010; Saleem et al., 2001; Takzare et al., 2009). The leaf of *A. vera* can be divided into gel and peel. The biological and toxicological effects of *A. vera* gel have been extensively studied. Gel formulations are used as functional food supplements, drugs and in cosmetics. *A. vera* peel, however, is usually discarded as industrial waste, even though it comprises over half of the leaf's weight. Considerable cost is incurred in discarding *A. vera* peel, which marginalizes the economic efficiency of the *Aloe* industry. *A. vera* peel could also contain some beneficial components.

For example, the yellow exudate portion between the gel and the peel is an abundant source of anthraquinones, which have antimicrobial and immunomodulatory properties (Liu et al., 2009; Pandey et al., 2010; Rodriguez et al., 2010). Indeed, it was reported that whole leaf extracts also have some therapeutic effects as well as the gel (Rodriguez et al., 2010). In this study, the antimicrobial, toxicological and immunomodulatory effects of *A. vera* peel extract *in vitro* and *in vivo* were examined.

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MATERIALS AND METHODS

Chemicals and instruments

Powder was made from *A. vera* peel solution using a freeze dryer (Bondiro, Korea) by first rapidly freezing the peel and then eliminating the water by sublimation. The phosphate buffered saline (PBS) used in this study had a final concentration of 137 mM sodium chloride, 2.7 mM potassium chloride, 4.3 mM sodium phosphate (dibasic, anhydrous) and 1.4 mM potassium phosphate (monobasic, anhydrous) in sterile solution. PBST (PBS with Tween 20) for the enzyme-linked immunosorbent assay (ELISA) was made by adding 0.05% Tween 20 to the PBS buffer solution. The substrate for ELISA was 3, 3', 5, 5'-tetramethylbenzidine (TMB), which is the most commonly used chromogen for horseradish peroxidase (HRP). The stop solution was 2N H_2SO_4.

Extraction of antimicrobial ingredients from *Aloe vera* peels

Among the various extraction methods for natural substances, one of the simplest ways of extraction, distilled water (DW), was used taking into consideration the economic use for industry (Waihenya et al., 2002).

Briefly, dried *A. vera* peel was obtained from the KJM Aloe R&D Center (Gyeonggi-do, Republic of Korea). 50 g of the peel was added to 500 ml of DW and was shaken (250 rpm) for 8 h at room temperature. The solution was centrifuged at 3000 rpm for 50 m. The supernatant was filtered through No. 5A filter paper (Advantec, Tokyo, Japan) and the filtered solution was freeze-dried again. 1 g of the dried powder was dissolved in 1.5 ml of DW to make a saturated solution.

The *in vitro* antimicrobial activity of *Aloe vera* peel extracts

34 bacterial strains including reference strains and isolates belonging to 9 genera were used to determine the *in vitro* antimicrobial effects of *A. vera* peel extract (Table 1). The bacterial strains used for testing the antimicrobial activities in this study were purchased from the American type culture collection (ATCC, Manassas, VA, USA), the Korea culture center of microorganisms (KCCM, Seoul, Korea), and the Korean collection for type cultures (KCTC, Taejon, Korea) or were isolated from raw milk, feces and meat samples. Antimicrobial resistant strains or virulent serotypes, which are public health issues, such as methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin resistant enterococci (VRE) and *Escherichia coli* O157:H7 strains were included in these tests (Altekruse et al., 1997; Rice, 2006; Sherman et al., 2010). Antimicrobial activity tests were done by first making a saline suspension of each organism at a density of 0.5 McFarland units. 5 µl of each bacterial suspension was inoculated into 50 µl of Muller-Hinton broth (MHB; Difco BRL, Detroit, MI, USA) in addition to 50 µl of the *A. vera* peel extract or DW (for control wells) into the wells of 96-well, flat bottomed plates (Nunc, Roskilde, Denmark). In the case of *Vibrio* spp., a tryptic soy broth (TSB; Difco) with 1% NaCl was used as the medium. After incubation at 37°C for 48 h, serial dilutions of the cultures were incubated on Petrifilm aerobic count plates (3 M, Minneapolis, MI, USA) at 37°C for 48 h, and the number of colonies was counted.

Animal

6 weeks old specific pathogen free ICR mice were purchased from Central Laboratory Animal (Seoul, Korea). Acute oral toxicity and *in vivo* antimicrobial activity tests for *A. vera* peel extracts were done on the ICR mice. The mice were kept at a temperature of 23±1°C and 50% humidity with an alternating 12 h light-dark cycle. Water and food were given *ad libitum* for 2 weeks before the experiment. This study was done in accordance with US guidelines (NIH publication #85-23, revised in 1985).

Acute oral toxicity test

20 male and female mice were randomly divided into 4 groups of 5. Each mouse was weighed. A dose of 5,000 mg/kg, corresponding to the United States Environmental Protection Agency (USEPA) standard for a nontoxic substance, was set as the highest dose (USEPA, 1998). Doses of 2,000 mg/kg according to the OECD test guideline 423 (OECD, 2000) and 1000 mg/kg were determined as the high dose and middle dose, respectively. The extract, freeze-dried powder dissolved in DW, was not prepared until just before administration and was given orally in consideration of future clinical applications.

Clinical signs including changes in general condition, toxic symptoms, and mortality were observed every hour for 6 h and once daily thereafter beginning the following day. The weight of all the mice was checked 1, 3, 8, 11 and 14 days post-administration. At the end of the 14 day testing period, all surviving mice were anesthetized by ether and euthanized by carbon dioxide inhalation. External and internal gross lesions were ascertained.

The *in vivo* antimicrobial effect of *Aloe vera* peel extracts

Salmonella enterica serovar Typhimurium DT104 was used to examine the *in vivo* antimicrobial activity of *A. vera* peel extracts. *S. typhimurium* DT104 is an ACSSuT type that is resistant to five antibiotics (ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline) (Witte, 2004). DT104 was cultured in TSB with shaking at 37°C for 24 h and harvested by centrifugation at 2,500 rpm for 30 m. The pellets were washed with PBS and resuspended in PBS. The suspension was used for the challenge experiments described next.To determine the *in vivo* antimicrobial activity of *A. vera* peel extracts, five groups of 10 female mice were randomly allocated (Figure 1). Two control (Ct) groups, Ct-DW and Ct-Aloe, were administered DW or *A. vera* peel extract, respectively, for 3 weeks without *S. typhimurium* DT104 challenge. The two challenge (Ch) groups, Ch-DW and Ch-Post, were both administered DW for 1 week before challenge, and then administered DW or *A. vera* peel extract for 2 more weeks, respectively.

Finally, the Ch-Both group was administered *A. vera* peel extract for 1 week before challenge and for 2 weeks after challenge. All of the administrations of DW (0.2 ml/mouse), *A. vera* peel extract (700 mg/kg, 0.2 ml/mouse) and challenge (3.7×10^9 colony forming units/ml of a *S. typhimurium* DT104 suspension, 0.1 ml/mouse) were done orally. Weight, clinical signs, and mortality of all the mice were examined every day. Samples of voided feces were collected from the Ch-DW, Ch-Post and Ch-Both groups for 5 days after challenge. The number of shed *S. typhimurium* in the collected fecal samples was counted (Kim et al., 2002). The IgG and IgA titers from the Ch-DW, Ch-Post, and Ch-Both groups were measured 1, 7, and 14 days post-administration. The serum IgG and fecal IgA titer were determined by ELISA according to Kim's method (Kim et al., 2002). Mice in the Ct-DW and Ct-Aloe groups were sacrificed at the end of the experiments, and their spleens were collected aseptically.

Splenocytes were cultured in the absence and presence of 5 µg/ml concanavalin A (ConA: Sigma-Aldrich, St. Louis, MO, USA) at 37°C for 48 h in a 5% CO_2 atmosphere. Cytokines including interleukin (IL)-2, IL-4, IL-10, and interferon-gamma (IFN-γ) were measured in the supernatants of the splenocyte cultures using

Table 1. Gram positive and negative bacterial strains used for the *in vitro* antimicrobial activity tests of *Aloe vera* peel extracts.

Gram staining	Genera and species	Strains*	Antimicrobial resistance or serotype†
Gram positive	*Staphylococcus aureus*	ATCC25923	-
	Staphylococcus aureus	SA 10	-
	Staphylococcus aureus	SA 11	-
	Staphylococcus aureus	SA 14	-
	Staphylococcus aureus	MR 03 26	MRSA
	Staphylococcus aureus	MR 03 24	MRSA
	Staphylococcus aureus	MR 03 25	MRSA
	Enterococcus spp.	ATCC29212	-
	Enterococcus spp.	Horse 25	-
	Enterococcus spp.	Feces 62	-
	Enterococcus spp.	Chicken 43	-
	Enterococcus spp.	03-1	VRE
	Enterococcus spp.	03-2	VRE
	Enterococcus spp.	03-3	VRE
	Bacillus spp.	Milk 7	-
	Bacillus spp.	Milk 14	-
	Bacillus spp.	Horse 10	-
Gram negative	*Escherichia coli*	Milk 62	-
	Escherichia coli	Milk 69	-
	Escherichia coli	Feces 26	-
	Escherichia coli	ATCC 35150	O157:H7
	Salmonella typhimurium	ATCC 13311	-
	Salmonella typhimurium	109	-
	Salmonella typhimurium	110	-
	Salmonella typhimurium	107	-
	Pseudomonas aeruginosa	Feces 25	-
	Pseudomonas aeruginosa	Milk 7	-
	Pseudomonas aeruginosa	Milk27	-
	Pseudomonas aeruginosa	Horse 17	-
	Vibrio vulnificus	KCTC 2980	-
	Vibrio vulnificus	KCTC 2912	-
	Vibrio parahaemolyticus	KCCM 41664	-
	Vibrio parahaemolyticus	KCTC 2729	-

*Reference strains were purchased from ATCC, KCCM, KCTC and KRA. †Methicillin resistant *Staphylococcus aureus,* MRSA; vancomycin resistant enterococci, VRE.

using the Ready-SET-Go ELISA Kit (eBioscience, San Diego, CA, USA) according to manufacturer's guidelines.

Statistical analysis

The data were analyzed by independent t-test using SPSS version 12.0.1 (SPSS, Chicago, IL, USA). $P<0.05$ was considered to be statistically significant.

RESULTS AND DISCUSSION

The *in vitro* antimicrobial activity of *A. vera* peel extracts was significantly apparent as seen by the decreased colony counts in the *Aloe*-treated groups compared with the untreated groups for all of the tested bacteria (Figure 2). Especially, the extract exhibited excellent antimicrobial activity against *E. coli* and *Vibrio* spp ($P<0.001$). Previous studies concerning the *in vitro* antimicrobial activity of *Aloe* spp. reported that *Aloe* extracts had antimicrobial activities against both Gram positive and Gram negative bacteria including *S. aureus*, *E. coli*, and *Klebsiella pneumonia* and that organic extracts of *Aloe*, including ethanolic or petroleum ether extracts, were more effective than aqueous extracts (Ndhlala et al., 2009; Pandey et al., 2010). The overall results from aqueous extracts are encouraging since for commercial use; moreover, such preparations are

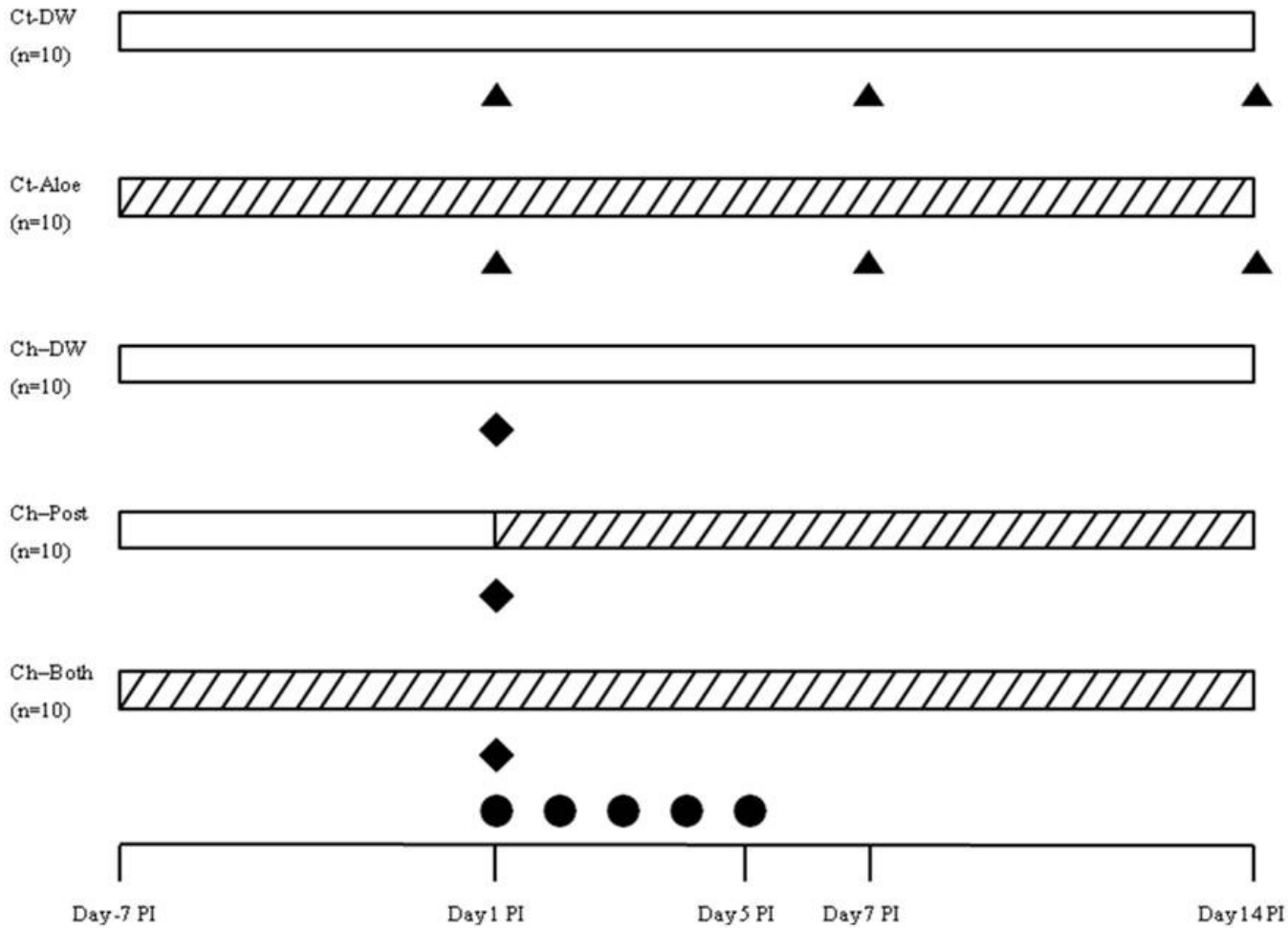

Figure 1. *In vivo* experimental design. Administration of aloe peel extracts (▨), challenge (◆), feces collection (●), and blood collection for antibody titer analysis (▲).

already used to provide veterinary disinfectants or as viable alternatives for antimicrobials. In the oral acute toxicity test, there were no mortalities in all of the groups including the highest dose group. A significant change in body weight was not evident in any of the groups. There was a slight decrease in body weight for the highest dose group on post-administration day 1, but it recovered thereafter to be on par with the other groups. Since the condition of the fecal samples for all of the groups was similar at day 1, the decreased body weight may have been associated with stress responses and slight dehydration. Clinical signs including dullness and ruffled hair were observed in both the experimental and control groups on day 1 but soon disappeared. At the end of the observation period, post-mortem examination was done. No significant lesions that could be linked to the *A. vera* peel extracts were evident. The data were consistent with the benign nature of the extract concerning toxicity. There were no significant changes in body weight, clinical signs, and mortality associated with the *A. vera* peel extracts during the testing period for *in vivo* antimicrobial activity.

The results of *S. typhimurium* DT104 fecal shedding counts are shown in Figure 3. After the challenge, a drastic decrease in fecal shedding was observed in the Ch-Post and Ch-Both groups compared to the Ch-DW group on day 1. On day 2, fecal shedding in the Ch-DW group also decreased but reversed by day 3 and increased until day 5. In the case of the two *Aloe*-treated groups (Ch-Post and Ch-Both groups), fecal shedding steadily declined and was significantly lower than the Ch DW group on day 5 ($P<0.05$). On day 5, fecal shedding was significantly different between the Ch-Both and Ch-Post groups, which suggest that a steady administration of the extract is more effective in combating infection. Although the shedding of *S. typhimurium* DT104 in the *Aloe*-treated groups was less than in the Ch-DW group, it was not completely eradicated. This suggests that *A. vera* peel extract might be useful as an additive effect in

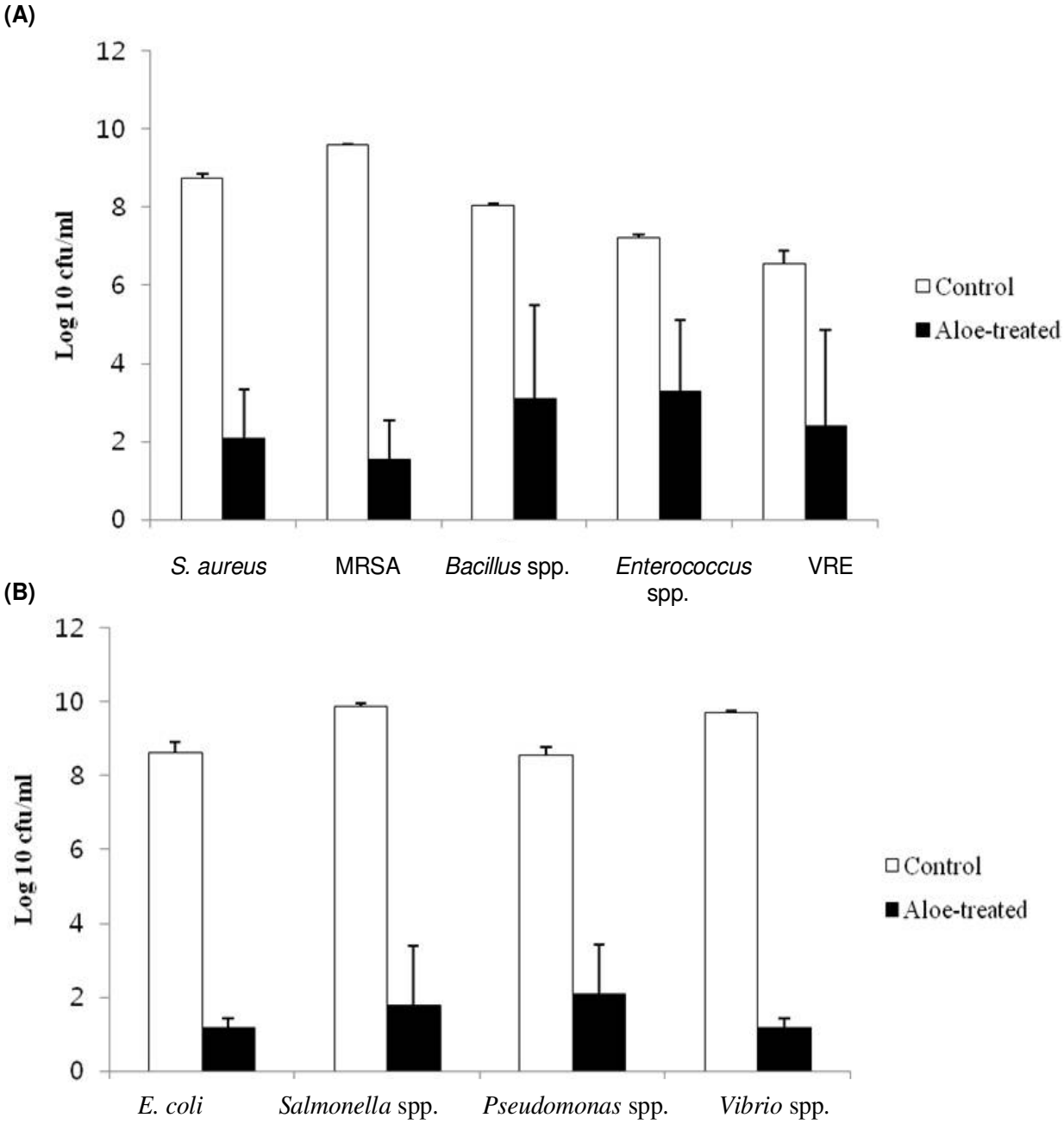

Figure 2. *In vitro* antimicrobial activity of *Aloe vera* peel extracts. Comparison of the results of the Petrifilm colony counting to (A) Gram-positive and (B) Gram-negative bacteria in the *Aloe*-treated group and untreated control group. MRSA, methicillin resistant *Staphylococcus aureus*; VRE, vancomycin resistant enterococci.

the treatment of infections. The immunomodulatory effects of *A. vera* peel extract was investigated. The level of serum *S. typhimurium* DT104-specific IgG was significantly higher in the Ch-Both group than in the Ct-DW and Ch-DW groups on day 14, and the highest concentration of IgG in the serum was evident in the Ch-Both group on day 7 (Figure 4A). A higher serum IgG level contributes to the prevention of the bacterial translocation and the resolution of bacteremia and septic shock (Zinner et al., 1976). The fecal IgA level of the Ch-DW, Ch-Post, and Ch-Both groups were significantly higher than the Ct-DW group on day 7, but the level was still significantly higher only in the *Aloe*-treated groups (Ch-Post and Ch-Both) than in the Ct-DW group on day 14 (Figure 4B). Fecal IgA indirectly represents secretory IgA released to the gut. IgA is an important antibody, especially on the mucosal surface where pathogens usually invade. The increased levels of IgG and IgA

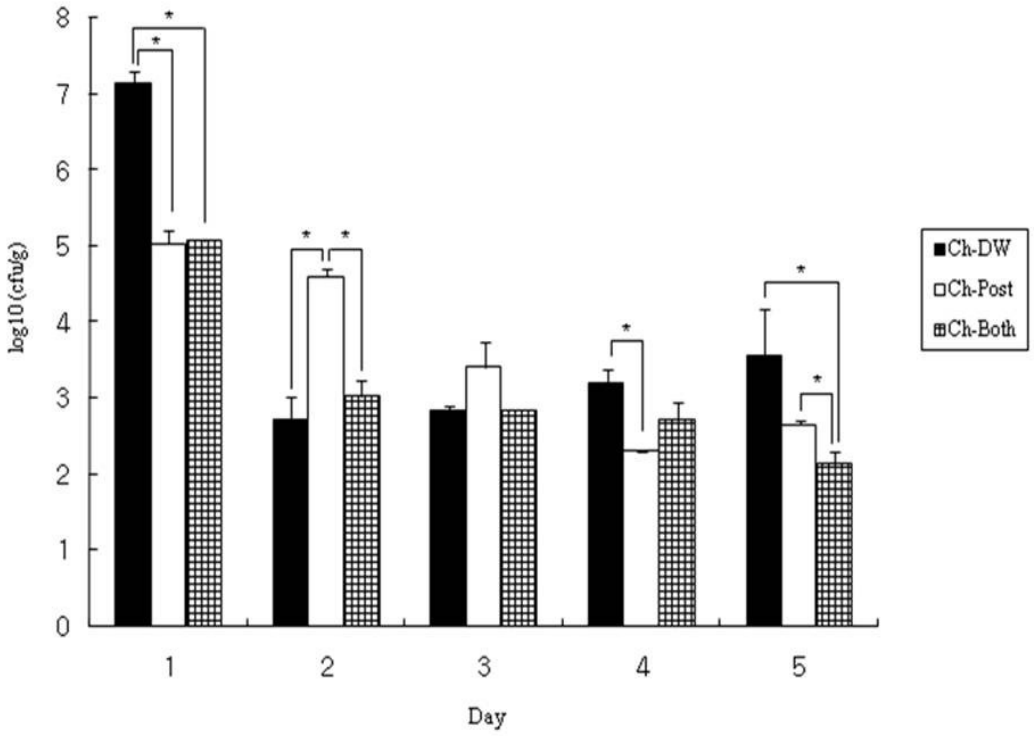

Figure 3. Viable *Salmonella typhimurium* DT104 in feces. *Significant difference (P <0.05).

specific to certain pathogens by the administration of the *A. vera* peel extract would strengthen the *in vivo* bactericidal activity. Furthermore, the higher levels of antibodies in the Ch-Both group compared to the Ch-Post group might indicate that continuous administration is effective in facilitating immune reactions.

In this study, the Th1 cytokines IL-2 and IFN-γ and the Th2 cytokines IL-10 and IL-4 were investigated. Regardless of ConA treatment, mouse splenocytes of the *Aloe*-treated groups produced significantly higher concentrations of IL-4 (P = 0.01 in untreated and P = 0.02 in ConA-treated wells) and IL-10 (P = 0.03 in untreated and P = 0.01 in ConA-treated wells) than those of the DW-treated group. However, the concentrations of IL-2 and IFN-γ were not significantly different between the *Aloe*-treated and DW-treated groups (Figure 5). IL-4 is an important cytokine in humoral immunity, which promotes the differentiation of precursor T cells to Th2 cell and increases the production of IgG_1 from B-lymphocytes (Nicola, 1994). In this study, increased IL-4 was concordant with higher antibody titers in the *Aloe*-treated groups. Moreover, IL-10 is a representative anti-inflammatory cytokine produced by Th2 cells (Florquin et al., 1994). IL-10, which is antagonist of Th1 cytokines, inhibits macrophages that produce IL-2, IL-6, and IFN-γ; in this study, the relatively lower IL-2 and IFN-γ levels were in accordance with the higher IL-10 levels. Th1 cytokines such as tumor necrosis factor-alpha (TNF-α), IFN- γ, IL-1, IL-2, and IL-6 are involved in septic shock and hyperinflammatory responses in salmonellosis and can result in a fatal outcome for the host (Bayston et al., 1990; Ribbons et al., 1997; Rongione et al., 1997). It has also been reported that the early production of IL-10 protects against lethal septic shock, while overproduced TNF-α and IFN-γ are detrimental in gram-negative bacterial infections (Barreiros et al., 2000). Consequently, the induced cytokine balance from *A. vera* peel extracts may be effective in eradicating salmonella infections and preventing septic shock caused by bacterial infections. Since *A. vera* contains active anthraquinones, including aloin and aloe-emodin, the antimicrobial and immune-modulatory effects of *A. vera* peel extracts were predictable. Anthraquinones are a structural analogue of tetracyclines that act by a similar mechanism Pandey et al., 2010).

Moreover, aloe-emodin has an immunomodulatory effect by promoting Th2 cytokines and reducing Th1 cytokines (Liu et al., 2009); in this study, these outcomes were evident. Since anthraquinones exist just beneath the peel of *A. vera* peels can be a source of these compounds at high concentrations. *A. vera* peel extracts may be an economic source of alternative supplementary agents for antimicrobials in the treatment of bacterial infections. This could reduce the use of antimicrobials. *A. vera* peel extract possesses antimicrobial activity both *in vitro* and *in vivo* and has immunomodulatory effects *in vivo* that include the elevated production of IgG and IgA and the promotion of anti-inflammatory cytokines.

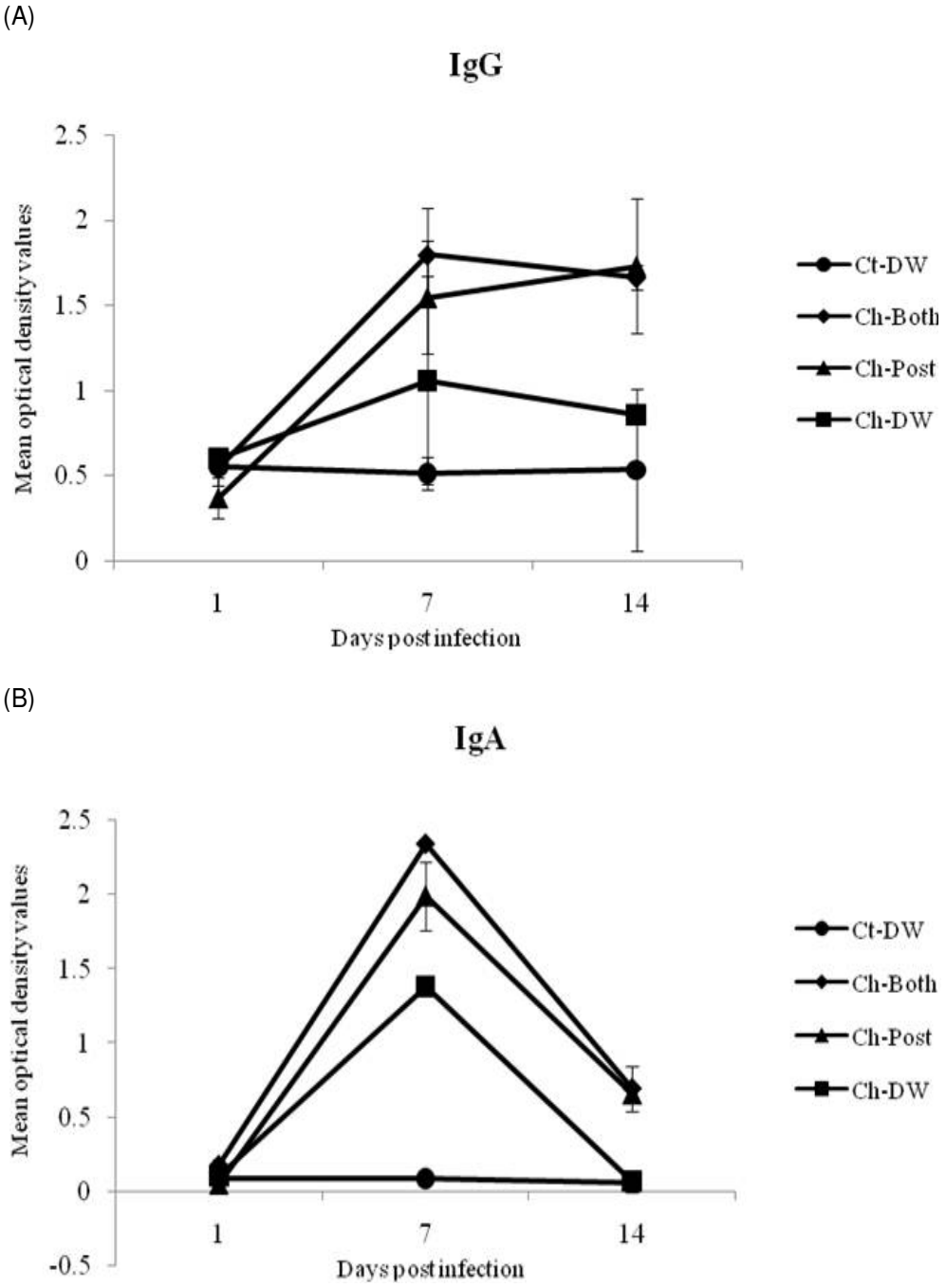

Figure 4. Serum IgG (A) and fecal IgA (B) titers.

These observed activities might be caused by the aloe-emodin, which exhibits antibacterial, anti-inflammatory, vasorelaxant, and anticancer activities. *A. vera* peel extracts and its antimicrobial and immunomodulatory effects suggest that the *A. vera* peel has an economical use as a natural antimicrobial supplement, which could be a good alternative to antimicrobial growth promoters banned in many countries. The practical use of the *A. vera* peel will be investigated in future studies.

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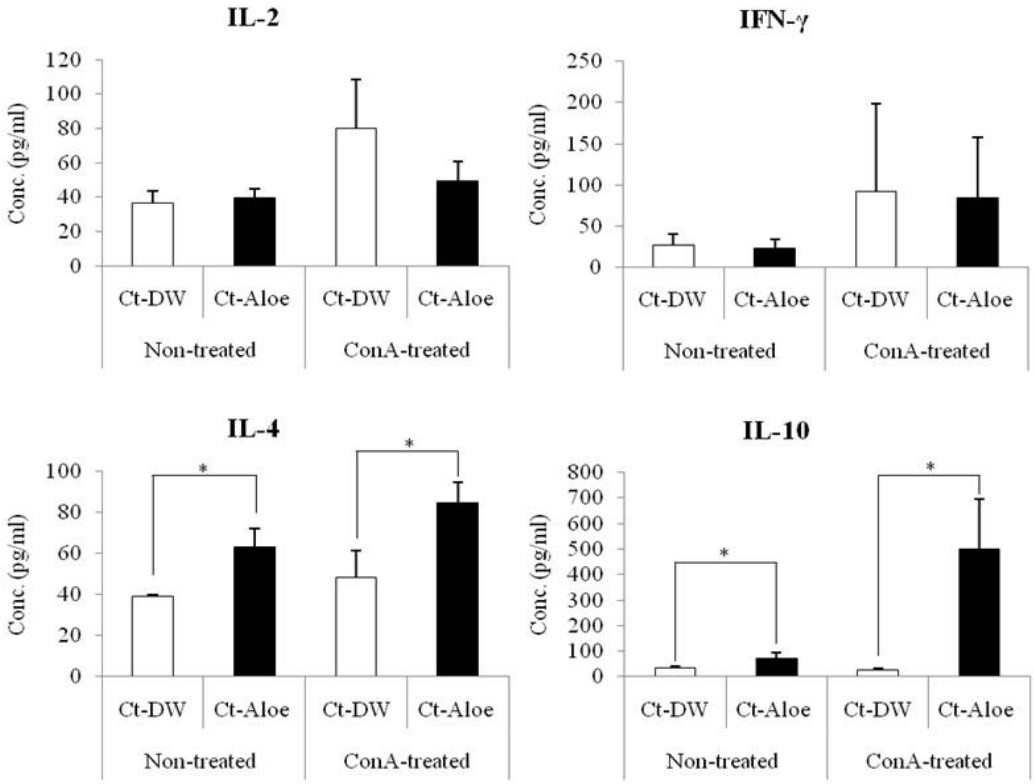

Figure 5. Production of the Th1 cytokines, IL-2 and IFN-γ, and the Th2 cytokines, IL-4 and IL-10 by splenocytes from mice treated with DW or *Aloe vera* peel extracts. *Significant difference (P <0.05).

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