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The Screening of Fermented Medicinal Herbs to Identify Those with Anti-inflammatory Properties

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ABSTRACT

Objectives : Consumption of fermented foods has been known to alleviate some of the symptoms of atopy and may limit allergy development, while there are also many medicinal herbs proved to be effective for immunologically-mediated diseases. In this study, we introduced modern zymology to ferment some herbs to see if fermentation has the possibility of increasing the anti-inflammatory effects of medicinal herbs. Interleukin-4 (IL-4) and interferon-gamma (INF-γ) have been demonstrated to be the main factors in the pathology of allergic diseases.

Methods : We measured the levels of IL-4 and INF-γ on concanavalin A-induced *BALB/c* mice spleen cells, which were subsequently treated with fermented and unfermented herbs. We then compared the fermented groups with unfermented groups to see if the anti-inflammatory effects of the herbs were influenced by fermentation.

Results and Conclusions : Our results showed that fermentation had the potential to increase the anti-inflammatory effects of some medicinal herbs, and *Astragalus membranaceus* and *Salvia miltiorrhiza* would be the most suitable medicinal herbs for fermentation among the herbs in this study.

Key words : Fermentation, Medicinal herb, Anti-inflammation, IL-4, INF-γ

Ⅰ. Introduction

The allergic diseases reflect an imbalance in lymphocyte-governed immunity, and it is dominated by the Th2 phenotype. Secretion of the cytokines IL-4, IL-5 and IL-13 by the allergen -sensitized Th2 cells recruits granular effector cells such as eosinophils, basophils and mast cells to the site of the allergic inflammation[1]. These effector cells, alone or in combination with cytophilic/reaginic IgE class antibodies, promote

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the clinical manifestations of allergy and atopy[2]. In addition, IL-4 and IL-13 promote B lymphocyte immunoglobulin isotype switching to IgE[3]. During the early stages of T lymphocyte differentiation, it is possible that the overexpression of a Th2 phenotype can be arrested by interferons[4], however the role in allergic diseases is still controversial. A recent paper reported that INF-γ enhanced airway hyperresponsiveness[5] and therapy of inhibiting INF-γ has been suggested as a new target in chronic asthma[6]. It has been also demonstrated that low levels of INF-γ prevent adhesion and migration of naive T and Th2 cells in vitro[7].

Long ago, fermentation was an archaic skill that was only used to make foods and wine, that was until the year 1857 when French chemist Louis Pasteur first connected yeast to fermentation. From that point on, zymology was introduced into many other fields and is now widely applied in food industry and pharmaceuticals industry. It is now understood that the lactic acid bacterium (LAB) present in fermented foods are primarily responsible for imparting health benefits, and various strains of dietary LAB have been shown to benefit a number of host physiological responses, including immune function[8-10]. Recently a number of researchers have attempted to apply zymology to medicinal herb pharmacy, and the results in their study is remarkable[11-18]. However, we think more studies are needed to prove the efficacy of the fermented herbs.

In this study, we used the method of modern zymology to ferment 7 different herbs which have been used frequently for the medical therapy of allergic diseases. To identify the fermented herbs that have anti-inflammatory properties, they were compared to the unfermented herbs by measuring their influences on the levels of IL-4 and IFN-γ.

Ⅱ. Materials and Methods

1. Animals

Female *BALB/c* mice (6 weeks old) purchased from ORIENT BIO INC. (Korea) were kept in the animal facility at the Department of Microbiology, College of Medicine, Kyunghee University.

2. Medicinal herbs

Astragalus membranaceus (AM, 黃芪)
Houttuynia cordata Thunb (HT, 魚腥草)
Liriope platyphylla (LP, 麥門冬)
Lonicera japonica Thunb (LT, 金銀花)
Opuntia dillenii Haw (OH, 白蓮草)
Platycodon grandiflorum (PG, 桔梗)
Salvia miltiorrhiza Bunge (SB, 丹蔘)

The extracted powders of AM, HT, LP, LT, PG, SB were obtained from Sun Ten Pharmaceutical Co. Ltd. (Taipei, Taiwan). OH was obtained from Nong-Lim Saeng Yak Co. Seoul, Korea, and the method of extraction was followed by a manual from Sun Ten Pharmaceutical Co. Ltd. (Taipei, Taiwan).

3. Bacteria strain and growing environment

The bacteria strain we used is *Lactobacillus casei PM1(KCCM10766P)*, and they were grown at 37 ℃ in Lactobacilli MRS Broth (Difco™, USA)

4. Process of fermentation

Lactobacillus casei inoculum cultured for 12 hours in MRS broth without beef extract were

added and were grown anaerobically in 10 ml basal medium (BM, 1% yeast extract, 0.5% peptone, 0.5% sodium cloride and 2% glucose) with 0.2 g sample extract powder in a shaking incubator. The growing temperature and the agitation speed of the culture were maintained at 37 ℃ and 180 rpm for 12 hours respectively. Fermented products were sterilized by autoclave. Further, it was centrifuged at 3000 × g and 4 ℃ for 15 minutes and the supernatant was recovered. The unfermented sample extract powders were manipulated with the same process without the inoculum. Basal mediums and herbal liquors, including fermented and unfermented ones were diluted to 0.01%, 0.05% and 0.1%, and they were stored at 4 ℃ until use.

5. Cell viability assay

The MTT assay was performed with Cell Proliferation Kit I (Roche, Germany). Spleen cells suspended in complete culture medium added on basal mediums and herbal liquors were cultured in a 96-well plates for 48 hours. Ten μl MTT labeling reagent was added to each well and the medium was incubated in a humidified atmosphere for 4 hours. One hundred μl solubilization solution was added and incubated in a humidified atmosphere overnight. The incubation temperature was maintained at 37 ℃. Concentration of the spleen cells was evaluated with the use of an ELISA reader at 550 - 600 nm wave length.

6. Cell culture and cytokine assay

Spleen cells from each mouse were isolated and suspended in complete culture medium (RPMI 1640 containing 10% FBS, 1% penicillin-streptomycin, and 1% glutamate). Cells (2×10^6/ml/well) were cultured in the plates with the presence of concanavalin A (Con A, 2μg/ml) and basal mediums or herbal liquors. Supernatants were collected after a 48 hours' culture period. IL-4 and IFN-γ concentrations in spleen cell culture supernatants were determined by ELISA (Enzyme-Linked Immuno -Sorbent Assay).

7. Data analysis

Basal mediums and herbal liquors were diluted to 0.01%, 0.05% and 0.1%. Each sample was measured by ELISA 3 times respectively, and the mean value was calculated. The final values were expressed as the percentage of the values that were measured from control group. The control group was the blank group that was neither treated by any basal medium nor herbal liquor.

Ⅲ. Results

1. Influence of basal mediums and herbal liquors on cell viability

There was no effect on inhibiting spleen cell viability in any of the basal mediums or herbal liquors, but most of them did enhance the cell proliferation(Fig. 1).

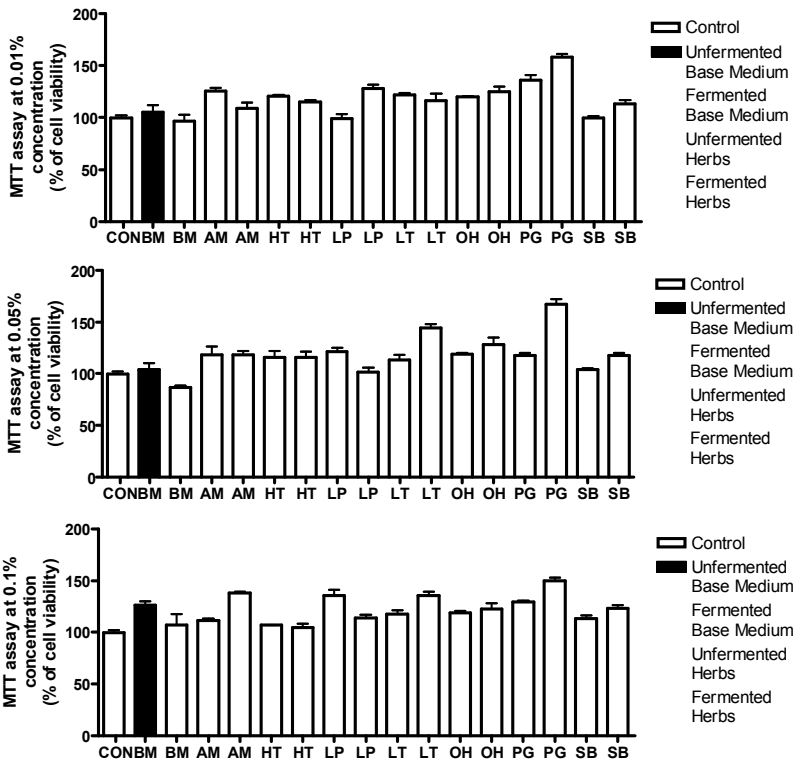

Fig. 1. Influence of basal medium and herb liquors on cell viability.

MTT assay was performed and the values were presented as the percentage of cell viability of control group. The control group was the blank group that was neither treated by any basal medium nor herbal liquor.

2. Comparison of fermented and unfermented herbs on IL-4 and INF-γ

At the 0.01% concentration, the level of IL-4 was 7.66% lower in the fermented basal medium than in the unfermented basal medium. At this concentration, the level of IL-4 were 26.29% lower for the *Astragalus membranaceus*, 50.68% lower for the *Opuntia dillenii Haw*, 26.97% lower for the *Platycodon grandiflorum* and 20.69% lower for the *Salvia miltiorrhiza Bunge*(Table 1).

At the 0.05% concentration, the level of IL-4 was 3.97% higher in the fermented basal medium than in the unfermented basal medium. However, at this concentration, the level of IL-4 were 32.22% lower for the *Astragalus membranaceus*, 34.46% lower for the *Houttuynia cordata Thunb*, 13.55% lower for the *Liriope platyphylla*, 39.73% lower for the *Opuntia dillenii Haw* and 8.35% lower for the *Salvia miltiorrhiza Bunge*(Table 1).

At the 0.1% concentration, the level of IL-4 was 4.75% lower in the fermented basal medium than in the unfermented basal medium. At this concentration, the level of IL-4 were 45.16% lower for the *Astragalus membranaceus*, 29.04% lower for the *Houttuynia cordata Thunb*, 26.72% lower for the *Liriope platyphylla*, 40.18% lower for the *Lonicera japonica Thunb* and 18.05% lower for the *Salvia miltiorrhiza Bunge*(Table 1).

At the 0.01% concentration, the level of INF-γ was 32.25% lower in the fermented basal medium than in the unfermented basal medium. At this concentration, the level of INF-γ were 22.81% lower for the *Astragalus membranaceus*, 31.17% lower for the *Liriope platyphylla*, 110.84% lower for the *Lonicera japonica Thunb*, 73.90% lower for the *Platycodon grandiflorum* and 60.26% lower for the *Salvia miltiorrhiza Bunge*(Table 1).

At the 0.05% concentration, the level of INF-γ was 19.79% higher in the fermented basal medium than in the unfermented basal medium. However, at this concentration, the level of INF-γ were 90.51% lower for the *Astragalus membranaceus*, 109.72% lower for the *Lonicera japonica Thunb*, 128.49% lower for the *Opuntia dillenii Haw*, 36.22% lower for the *Platycodon grandiflorum* and 99.56% lower for the *Salvia miltiorrhiza Bunge* (Table 1).

At the 0.1% concentration, the level of INF-γ was 28.03% lower in the fermented basal medium than in the unfermented basal medium. At this concentration, the level of INF-γ were 327. 64% lower for the *Astragalus membranaceus*, 2570.80% lower for the *Houttuynia cordata Thunb*, 177.06% lower for the *Lonicera japonica Thunb*, 322.55% lower for the *Opuntia dillenii Haw* and 216.07% lower for the *Salvia miltiorrhiza Bunge*(Table 1).

Table 1. The effect of basal mediums and herbal liquors, including fermented and unfermented ones, on the levels of IL-4 and INF-γ.

Name of Herb	Method	Percentage of IL-4 (%)			Percentage of INF-γ (%)		
		Concerntration			Concerntration		
		0.01%	0.05%	0.1%	0.01%	0.05%	0.1%
Basal Medium (BM)	Unfermented	101.74*	79.10	74.95	140.28	92.67	140.49
	Fermented	94.08	83.07	70.20	108.03	112.46	112.46
Astragalus membranaceus (AM, 黃芪)	Unfermented	95.41	99.19	106.73	56.48	161.82	436.43
	Fermented	69.12	66.97	61.57	33.67	71.31	108.79
Houttuynia cordata Thunb (HT, 魚腥草)	Unfermented	66.58	97.08	104.62	143.64	265.91	2852.06
	Fermented	92.64	62.62	75.58	330.56	280.62	281.26
Liriope platyphylla (LP, 麥門冬)	Unfermented	62.42	89.12	95.83	80.76	73.02	125.35
	Fermented	71.27	75.57	69.11	49.587	98.54	176.88
Lonicera japonica Thunb (LT, 金銀花)	Unfermented	65.76	90.38	116.81	120.26	121.53	322.84
	Fermented	83.07	90.43	76.63	9.42	11.81	145.78
Opuntia dillenii Haw (OH, 白蓮草)	Unfermented	110.08	116.39	97.50	147.16	312.34	378.99
	Fermented	59.40	76.66	113.65	168.24	183.85	56.44
Platycodon grandiflorum (PG, 桔梗)	Unfermented	95.01	60.75	79.52	116.75	213.30	626.09
	Fermented	68.04	81.99	93.70	42.85	177.08	942.15
Salvia miltio-rrhiza Bunge (SB, 丹蔘)	Unfermented	88.73	69.92	82.86	90.80	146.97	305.08
	Fermented	68.04	61.57	64.81	30.54	47.41	89.01

*The values were expressed as the percentage of the values that were measured from control group. The control group was the blank group that was neither treated by any basal medium nor herbal liquor.

Ⅳ. Discussion

Many studies have demonstrated that certain traditional medicinal herbs have therapeutic benefits in immunologically mediated diseases. We selected *Astragalus membranaceus*[19], *Houttuynia cordata Thunb*[20], *Liriope platyphylla*[21], *Lonicera japonica Thunb*[22], *Opuntia dillenii Haw*[23], *Platycodon grandiflorum*[24] and *Salvia miltiorrhiza Bunge*[25] in our study, which have been used frequently for medical therapy of allergic diseases. Yet over the last decade, there has been an accumulation of evidence that the consumption of fermented foods can alleviate some of the symptoms of atopy and may limit allergy development[26]. To see if fermentation increases the effects of medicinal herbs on antiinflammation, we used method of modern zymology to ferment 7 different herbs, and checked by measuring the levels of IL-4 and INF-ɣ, which are considered to be the main factors in the pathology of allergic diseases.

In animal models, lactic acid bacteria (LAB) has been shown to reduce allergen-stimulated production of IL-4 in some cases[27]. To avoid the influence of LAB when measuring the levels of IL-4 and INF-ɣ, fermented products were sterilized by autoclave. However, we found that both fermented and unfermented basal mediums still influenced the levels of IL-4 and INF-ɣ. For the fermented and unfermented basal mediums, the levels of IL-4 were inhibited in all of the concentrations except the 0.01% concentration unfermented basal medium, and the levels of INF-ɣ were enhanced in all of the concentrations except the 0.05% concentration unfermented basal medium. When compared with unfermented basal medium, the levels of IL-4 were lower in fermented basal medium at 0.01% and 0.1% concentration, and we found the same result in the levels of INF-ɣ(Fig. 2, Table 1).

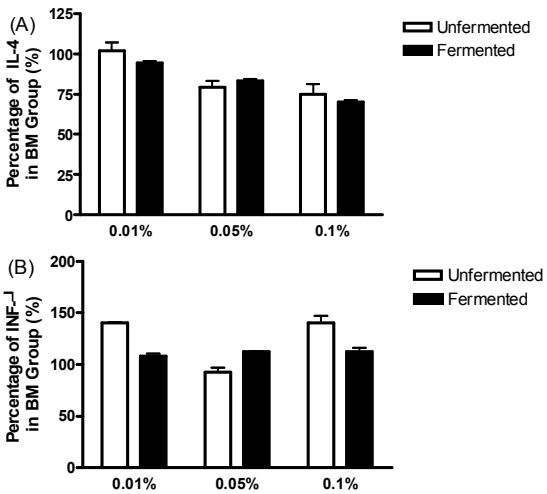

Fig. 2. Comparison of the effects on IL-4 (A) and INF-ɣ (B) between unfermented and fermented basal medium (BM). Basal mediums were diluted to 0.01%, 0.05% and 0.1%.

Each sample was measured by ELISA 3 times respectively, and the mean value was calculated. The final values were expressed as the percentage of the values that were measured from the control group. The control group was the blank group that was neither treated by any basal medium nor herbal liquor.

When excluding the influence of the basal mediums, we found that fermented *Astragalus membranaceus* and *Salvia miltiorrhiza Bunge* inhibited the levels of IL-4 at all of the concentrations and the values were all lower than those of the unfermented pairs(Fig. 3, Table 1).

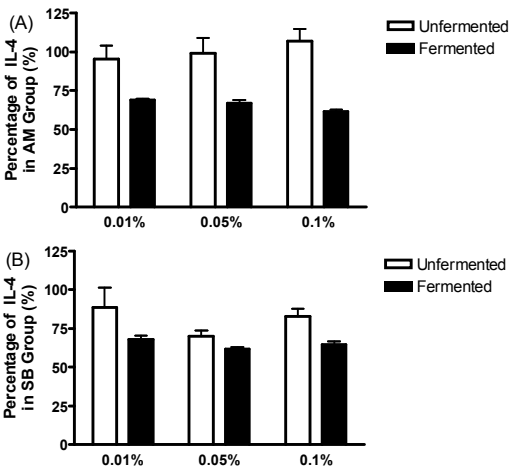

Fig. 3. Comparison of the effects on IL-4 between unfermented and fermented herbal liquors.

Herbal liquors were diluted to 0.01%, 0.05% and 0.1%. Each sample was measured by ELISA 3 times respectively, and the mean value was calculated. The final values were expressed as the percentage of the values that were measured from the control group. The control group was the blank group that was neither treated by any basal medium nor herbal liquor. (A) *Astragalus membranaceus* [AM], (B) *Salvia miltiorrhiza Bunge* [SB]

IL-4 can recruits granular effector cells such as eosinophils, basophils and mast cells to the site of allergic inflammation [1], and promote B lymphocyte immunoglobulin isotype switching to Ig E [3]. So IL-4 is considered to be the most important factor in the pathology of allergic inflammation. From the results of this study, we found that the levels of IL-4 were decreased by each of the fermented herbs at at least one of the tested concentrations. More over, *Astragalus membranaceus* and *Salvia miltiorrhiza Bunge* decreased the levels of IL-4 at all of the concentrations.

On the other hand, we found that *Astragalus membranaceus*, *Lonicera japonica Thunb* and *Salvia miltiorrhiza Bunge* decreased the levels of INF-γ at all concentrations after fermentation. However, we did not find any herb that increased the level of INF-γ at all concentrations after fermentation(Fig. 4, Table 1).

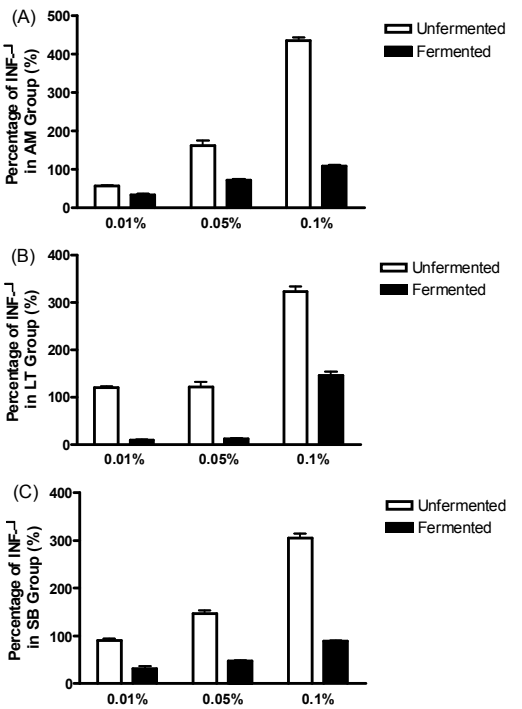

Fig. 4. Comparison of the effects on INF-γ between unfermented and fermented herbal liquors.

Herbal liquors were diluted to 0.01%, 0.05% and 0.1%. Each sample was measured by ELISA 3 times respectively, and the mean value was calculated. The final values were expressed as the percentage of the values that were measured from the control group. The control group was the blank group that was neither treated by any basal medium nor herbal liquor. (A) *Astragalus membranaceus* [AM], (B) *Lonicera japonica Thunb* [LT], (C) *Salvia miltiorrhiza Bunge* [SB]

INF-γ can promote Th1-type immune responses and reduce Ig E production[28], however as previously mentioned, the role of INF-γ in allergic diseases is still controversial. Recent studies have shown that low levels of INF-γ prevent adhesion and migration of naive T and Th2 cells in vitro [7], and therapy of inhibiting INF-γ has been suggested as a new target in chronic asthma [6]. We found that *Astragalus membranaceus* and *Salvia miltiorrhiza*, which decreased the levels of IL-4 after fermentation, also decreased the levels of INF-γ. So we suggested that *Astragalus membranaceus* and *Salvia miltiorrhiza* down-regulate both Th1 and Th2, which is defined as the immune suppressive response, to promote the effect on antiinflammation.

In conclusion, fermentation has the potential to increase the anti-inflammatory effects of some medicinal herbs, and we found *Astragalus membranaceus* and *Salvia miltiorrhiza* would be the most suitable medicinal herbs for fermentation among the herbs in this study. We suggest that further investigations should be done, and if we could find the best fermentation conditions and concentrations, we would be able to produce the most effective fermented medicinal herbs, and this would be helpful for traditional therapy in the clinic.

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