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Antioxidant and Anti-inflammatory Activities of Agricultural By-products and Medicinal Herbs; As Potential Functional Animal Products

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ABSTRACT

The aim of this study was to determine theantioxidant and the anti-inflammatory activities of agricultural by-products and medicinal herbs to assess the potential for functional animal products. Toestimate the antioxidant and anti-inflammatory activities of agricultural by-products and medicinal herbs, we performed water extraction of the agricultural by-products and herbs, and examined the activity using colorimetric assay. In addition, we also determined the effect of the agricultural by-products and herbs on iNOS and COX-2 expression in macrophage cells.All of the agricultural by-products and herbs exhibited antioxidant and anti-inflammatory activities in a dose-dependent manner and higher anti-inflammatory activities than antioxidant activities.Among the agricultural by-products and herbs, *Nelumbonucifera*(NN) showed the strongest antioxidant activity (75.28%), and*Rosmarinusofficinalis*(RO)exhibited the highest anti-inflammatory activity, and inhibited 90.28% of NO production against the control group. Moreover, the expressions of iNOS and COX-2 were reduced in the agricultural by-products and herbs treated-groups. These results give the understanding of biological activities of the agricultural by-products and medicinalherbs, and help to develop functional feed for production of safer and healthier animal products.

Keywords: Anti-inflammatory activity,Antioxidant activity, Agricultural by-products, Colorimetric assay, Medicinal herbs

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INTRODUCTION

Recently, several universal trends in consumer attitudes to health and food have been identified. Consumers are increasingly concerned about health and safety as well as quality of meat products and the demand for these products is increasing [9]. On the other hand, one of the biggest challenges for the animal feed industry will be to meet the growing demand in animal protein in light of increased cost of feed ingredient as well as tougher restrictions on the use of antimicrobial growth promoters imposed by consumers and governments[11]. For above reason, the effective functional feed that enhance the immune system are desired.

Acute inflammation is part of the defense response, but chronic inflammation has been found to mediate several diseases, including cardiovascular diseases, cancers, diabetes, arthritis, Alzheimer's disease, pulmonary diseases, and autoimmune diseases. Inflammation leads to up-regulation of a series of enzymes in affected areas. Inducible nitric oxide synthase (iNOS) catalyzes the formation of nitric oxide (NO) from L-arginine. High concentrations of NO have been found to play important roles in inflammation and carcinogenesis[25]. iNOS can be induced by bacterial endotoxic LPS, interferon-γ (IFN-γ), and a variety of pro-inflammatory cytokines [5, 25]. Meanwhile, ROS production by H_2O_2 activates the inflammasome which can promote inflammatory responses[16]. ROS may either directly trigger inflammasome assembly or be indirectly sensed through cytoplasmic proteins that modulate inflammasome activity[16]. From the viewpoint of cellular biology, accordingly, chronic inflammation accompanied by oxidative stress is linked to various steps involved in many diseases mentioned above [12].

Medicinal plants have long been recognized as remedies and important sources of treatment for developing countries [21]. Ginger extract inhibited the production of NO and prostaglandin E2 (PGE2), as well as iNOS expression in cultured cell model [3]. Also, it has been reported that the extracts from strawberry, loquat, mulberry and bitter melon juice decreased the secretion of pro-inflammatory cytokines and up-regulated the secretion of anti-inflammatory cytokine such as IL-10 in LPS-stimulated macrophages [12].Public interest in complementary and alternative therapies, including the use of botanical dietary supplements and agricultural by-products has witnessed spectacular rise throughout the world. Indeed, knowledge of the therapeutic and nutritional properties of several plant extracts and isolated compoundspredates recorded history [1, 14, 15, 20].

Therefore, the present study was undertaken to investigate both antioxidantand anti-inflammatory activities ofthe agricultural by-products andmedicinal herbs as potential functional feed to produce safer and healthier animal products.

MATERIALS AND METHODS

Materials

Agricultural by-products (*Ginseng radix rubra* marc, residue of red ginseng: GM; *Panax ginseng* marc,residue of ginseng:PM; *Camellia sinensis* marc, residue of green tea; CM) and 14 kinds of medicinal herbs (*Brassica oleracea var. italic*, cabbage: BI; *Nelumbonucifera*,lotus:

NN; the root of *Nelumbonucifera*, lotus root: RNN; *Cymbopogon citrates*, lemongrass:CC; *Brassica oleracea var. botrytis*, cauliflower:BB; *Allium tuberosum*, chives:AT; *Rosmarinusofficinalis*,rosemary: RO; *Capsicum annuum*, red pepper: CA; *Menthapiperita*, peppermint:MP; *Apiumgraveolens*, celery: AG; *Chrysanthemum zawadskii var. latilobum*, Siberian chrysanthemum:CL; *Ocimumbasilicum*, basil: OB; *Allium sativum*, garlic: AS; *Lavandulaofficinalis*, lavender: LO)were obtained from local food market (Chungju, Korea). Dulbecco's Modified Eagle Medium (DMEM), fetal bovine serum (FBS), penicillin-streptomycin were obtained from Invitrogen Corporation (Carlsbad, CA). Lipopolysaccharide (LPS) from Escherichia coli (serotype 0127:B8) and *tetra*-butyl hydroperoxide (*t*-BHP) were procured from Sigma Aldrich (St. Louis, MO, USA). All other reagents were of the highest grade available commercially.

Preparation of extraction from agricultural by-products and medicinal Herbs

1L of deionized water was added to 1 kg of each sample, and the mixture was heated at 100°C for 2 h. The mixture was then rapidly cooled to 20~25°C in an ice bath. The extracts were lyophilized in a freeze drier for 3 daysand stored at -20°C until use.

Cell culture

RAW264.7, a mouse macrophage cell line, and Chang, normal liver cell line obtained from American Type Culture Collection (ATCC, Rockville, MD, USA), was cultured in DMEM supplemented with 10% heat-inactivated FBS and 1% antibiotics in 5% CO_2, 95% air and humidified atmosphere at 37 °C.

MTT assay

Cell viability was determined by using the MTT assay. In brief, Chang cells were seeded at 0.5×10^6 cells per well in 96-well microtiter plates in complete medium. After incubation for 24 h, 200 µl of each extracts with or without 80 µM of *t*-BHP in DMEM was transferred to the well to give final concentrations ranging from 0 to 1.0 mg/ml. Following incubation for 24 h with each sample, the culture medium was aspirated and 200 µl of MTT dye solution (0.5 mg/ml) was added to each well. After incubation for 4 h, the medium was aspirated, and the purple crystals were dissolved with dimethyl sulfoxide. The absorbance in each well was measured at 540 nm using a microplate reader. The antioxidant activity was expressed as:

$$\text{Antioxidant activity (\%)} = \{1-(OD_S-OD_0)/(OD_C- OD_0)\}\times 100$$

where, OD_S is the absorbance of the DMSO solution from the sample and *t*-BHP-treated cells; OD_0 is the absorbance of the DMSO solution itself; OD_C is the absorbance of the DMSO solution from *t*-BHP-treated cells at 540 nm, respectively.

NO inhibitory activity

The RAW264.7 cells were seeded in a 96 well-plate and incubated with each herb extracts in the presence or absence of LPS (100ng/ml) for 24 h. The culture supernatant (100

µl) was mixed with Griess reagent (100 µl, 1% sulphanilamide, 0.1% N-1-naphthyl ethylenediamine) for 10 min and the absorbance was measured at 550 nm. A standard curve was constructed using known concentrations of sodium nitrite. The anti-inflammatory activity was expressed as:

$$\text{Anti-inflammatory activity (\%)} = \{(OD_C\text{-}OD_0)\text{-}(OD_S\text{-}\ OD_0)\}/(OD_C\text{-}OD_0) \times 100$$

where, OD_C is the absorbance of the Griess reagent itself; OD_S is the absorbance of the Griess reagent from the sample and LPS-treated cells; OD_0 is the absorbance of the Griess reagent from LPS-treated cells at 550 nm, respectively.

Western blottinganalysis

The total cell lysate was electrophoresed on 10% sodium dodecyl sulfatepolyacrylamide gel electrophoresis (SDS–PAGE) and transferred to an immobile polyvinylidene fluoride membrane (Millipore, Billerica, MA). The membrane was blocked with 5% skim milk for 1 h, washed, and then incubated overnight at 4°C with the primary antibodies. All antibodies were purchased from Santa Cruz Biotechnology Inc. (Santa Cruz, CA). After the membranes were washed in TBS-T, secondary antibody reactions were performed with an appropriate source of antibodies labeled with horseradish peroxidase for 90 min at room temperature. After application of the secondary antibody, over the triplicate washes were followed with TBS-T, and developed for visualization using an ECL detection kit by Luminescent image analyzer (LAS-3000, Fujifilm, Tokyo, Japan).

Statistical analysis

All data were presented as the means ± standard errors of means (SEM), and statistical analyses were performed for 3 times for all experimental items.

RESULTSAND DISCUSSION

Functional feeds imply the feed that provide other benefits than those merely nutritional. The underlying concept of a functional feed is that of a feed or those components, having the ability to contribute beneficially to produce safer and healthier animal products by way of improving the state of well-being and reducing the risk of disease for domestic animal. Therefore, we investigated both anti-inflammatory and antioxidant activities of the agricultural by-products andmedicinal herbs as potential functional feed additives.

Antioxidant activities

The antioxidant activities of the agricultural by-products and medicinal herbs were evaluated using MTT assay. As shown in Table 1, 9 kinds of herbs showed the antioxidant activity with over 20%. Among them, NN showed the strongest antioxidant activity (75.275%) at 1.0 mg/ml, and the value of necessary concentration of extracts to reduce in 50 percent (EC_{50}) DPPH is 0.092 mg/ml. The activities of other herbs declined as follows: CA (69.547%) > NN(35.986%) > CC(34.706%) > CM(29.786%) > AT, AG(27.832%) > LO(22.508%) >

MP(20.891%) in a dose-dependent manner (Table 2). In a previous study, it was reported that pretreatment with eugenol significantly attenuated liver damage, reduced the lipid peroxidation and protein oxidation as indicated by the decreased levels of TBARS and maintained the antioxidant status to normal value in rats[26]. Also, He et al. [8] indicated that *Meconopsisquintuplinervia* extract exhibited strong *in vitro* and *in vivo* antioxidant activities. These results suggest that the extracts of medicinal plants and herbs are valuable source of natural antioxidants.

Table 1: Antioxidant activities (%) of the by-products and herbs

Concentrations (μg/ml)	CL[1]	RO	LO	CC	MP	OB	CA	AT	BI
1000	13.2±1.0	19.0±2.0	22.5±3.8	34.7±2.7	20.9±2.5	18.2±1.9	69.6±6.9	27.8±3.9	14.8±1.4
500	13.1±1.6	18.1±2.5	18.6±1.3	16.2±1.2	20.6±3.5	17.2±1.9	26.1±1.5	13.8±2.4	13.0±1.3
250	11.7±0.3	17.7±1.8	18.3±1.5	12.9±1.5	16.3±1.6	15.8±1.4	22.9±1.3	12.8±4.2	13.2±1.2
100	11.1±1.5	14.0±2.6	14.7±1.0	11.7±1.0	14.0±1.0	13.7±1.7	15.1±2.6	11.5±3.0	11.9±1.1
50	10.9±0.9	11.9±2.8	14.2±1.7	11.5±1.5	13.0±1.5	12.7±1.2	11.0±1.0	10.6±1.4	11.8±1.1
10	10.5±1.5	11.1±1.3	12.4±1.8	11.4±1.0	12.7±1.0	12.3±1.5	10.5±1.7	10.5±2.9	11.9±1.1
1	10.5±1.5	10.9±1.0	10.9±2.7	11.2±1.6	10.9±1.5	10.9±0.8	10.4±2.5	10.2±1.5	11.2±1.1
0.1	9.9±1.2	9.9±2.3	10.5±0.8	11.0±1.2	9.7±1.4	10.5±1.7	10.2±1.9	9.9±2.0	11.0±1.0
Concentrations (μg/ml)	BB		AG	AS	NN	RNN	PM	GM	CM
1000	13.4±1.2		27.8±1.5	12.7±1.9	75.3±5.5	36.0±3.4	13.3±2.0	11.0±1.1	29.8±2.5
500	12.7±1.2		21.9±3.5	11.5±1.4	73.8±6.3	15.1±1.5	11.0±2.5	10.7±0.9	17.5±2.0
250	11.3±1.0		11.3±1.5	11.4±1.8	41.2±4.1	14.7±1.3	10.7±1.4	10.7±1.2	15.8±1.0
100	11.1±1.5		10.9±2.0	11.3±1.5	15.4±1.4	13.6±1.4	10.3±1.0	10.6±1.4	14.6±1.8
50	10.9±1.1		10.3±1.1	11.3±1.0	12.8±1.2	12.0±1.0	9.7±1.5	10.6±1.0	13.5±1.5
10	10.6±1.1		10.2±1.0	11.1±1.7	12.3±1.2	11.3±1.2	9.5±0.9	10.5±0.8	12.3±1.7
1	10.5±1.4		10.2±2.1	10.5±1.3	11.8±1.5	11.2±1.9	9.4±1.5	10.4±1.4	11.4±1.3
0.1	10.4±1.6		9.6±1.4	10.4±2.0	12.5±1.1	11.1±1.1	9.2±2.0	10.4±1.3	10.7±1.9

Data are mean ±SEM values (n = 3).
[1]CL: *Chrysanthemum zawadskii var. latilobum*, RO:*Rosmarinusofficinalis*, LO:*Lavandulaofficinalis*, CC:*Cymbopogon citrates*, MP:*Menthapiperita*, OB:*Ocimumbasilicum*, CA: *Capsicum annuum*, AT: *Allium tuberosum*, BI: *Brassica oleracea var. italic*, BB: *Brassica oleracea var. botrytis*, AG:*Apiumgraveolens*, AS: *Allium sativum*, NN:*Nelumbonucifera*, RNN: root of *Nelumbonucifera*, PM:*Panax ginseng* marc, GM: *Ginseng radix rubra* marc, CM: *Camellia sinensis* marc

Anti-inflammatory activity

It is well known that LPS alone can induce mRNA expression and protein synthesis of iNOS and NO production in RAW264.7 macrophage cells [10].Also, it was reported that over production of NO and its derivatives including peroxynitrite and nitrogen dioxide are found to be provoke the pathogenesis of septic shock and diverse autoimmune disorders [13]. In this study, we estimated anti-inflammatory activity of the agricultural by-products and medicinal herbs by using NO inhibitory activity assay.As shown in Table 2, it was observed the anti-inflammatory activity at 1 mg/ml followed the order RO (90.281%) >CC (87.547%) >NN (83.904%) >CL (80.561%) >CM (79.043%) >RNN (78.131%)in a dose-dependent

manner.It was reported that carnosol, the purified constituent of rosemary, inhibited NO production in LPS-activated murine peritoneal macrophages and RAW 264.7 cells [2].Similarly, Peng et al. [18] reported that rosemary leaves extracts showed a potential anti-inflammatory effect by reducing NO production.

Table 2: Anti-inflammatory activities (%) of the by-products and herbs

Concentrations (μg/ml)	CL[1]	RO	LO	CC	MP	OB	CA	AT	BI
1000	80.5±4.3	90.2±4.5	70.5±4.5	87.5±4.5	71.4±4.0	47.7±2.7	69.5±5.0	48.6±3.5	34.4±3.0
500	60.8±4.0	34.6±2.9	43.9±3.6	41.0±4.0	32.8±2.7	38.9±1.7	31.3±1.7	38.3±2.5	32.5±2.9
250	48.0±2.0	33.7±2.8	39.2±3.0	37.1±2.7	29.5±1.7	38.3±2.6	28.6±1.7	35.6±3.2	20.1±1.7
100	37.4±1.2	33.4±3.0	37.3±1.9	28.9±2.1	4.9±2.1	32.2±2.1	28.3±2.0	34.6±2.1	3.4±0.4
50	24.0±1.6	29.8±1.8	37.4±2.3	20.7±1.8	-	31.9±2.7	23.7±1.4	26.4±1.9	-
10	-	25.5±1.0	-	7.6±0.4	-	26.8±1.3	10.7±0.4	24.9±1.3	-
Concentrations (μg/ml)	BB	AG	AS	NN	RNN	PM	GM	CM	
1000	28.0±2.1	38.0±2.0	41.6±3.5	83.9±8.1	78.1±7.1	71.7±4.0	36.5±1.8	79.0±4.5	
500	26.8±2.0	27.7±1.0	39.8±2.0	48.9±4.2	33.1±3.1	34.6±1.2	24.3±2.0	49.5±2.0	
250	24.9±1.0	23.7±1.9	35.1±1.8	34.0±2.7	31.3±4.0	32.2±2.4	19.2±1.0	33.4±2.0	
100	14.6±1.0	8.8±4.0	33.1±1.5	32.8±3.0	29.2±1.4	31.9±1.2	7.6±0.1	24.0±1.7	
50	-	-	32.8±1.3	3.2±0.1	16.1±0.5	28.0±1.8	-	18.9±0.9	
10	-	-	-	-	11.0±0.9	8.2±4.0	-	14.3±0.7	

Data are mean ±SEM values (n = 3).
[1]CL: *Chrysanthemum zawadskii var. latilobum*, RO:*Rosmarinusofficinalis*, LO:*Lavandulaofficinalis*, CC:*Cymbopogon citrates*, MP:*Menthapiperita*, OB:*Ocimumbasilicum*, CA: *Capsicum annuum*, AT: *Allium tuberosum*, BI:*Brassica oleracea var. italic*, BB:*Brassica oleracea var. botrytis*, AG:*Apiumgraveolens*, AS:*Allium sativum*, NN:*Nelumbonucifera*, RNN:root of *Nelumbonucifera*, PM:*Panax ginseng* marc, GM:*Ginseng radix rubra* marc,CM:*Camellia sinensis* marc

Correlation between anti-inflammatory and antioxidant activity of the medicinal herbs

In general, it has been well known that many natural plants and herbs possessing polyphenolic compounds with antioxidant activities also have anti-inflammatory activities. On the other hand, inflammatory response and oxidative damage are major factors including cardiovascular ad neurodegenerative diseases, while herbal polyphenolic compounds are capable of reducing such risk factor[6]. In the present study, all of the medicinal herb extracts exhibited higher anti-inflammatory activities than the antioxidant activities, andthe anti-inflammatory activities showed over 28.02%, on the contrary, only 9 herbs possessed the antioxidant activities with over 20%. We assume that it is due to stimulateconcentrations, therefore, there are possibility that if the *t*-BHP concentration were reduced, the antioxidant activities could be higher than the presented results.

In the present study, we classified the medicinal herbs into 3 groups. Group A refers that the medicinal herbs show low antioxidant activity (below 45% at 1.0 mg/ml) and high anti-inflammatory activity (over 60% at 1.0 mg/ml), group B implies that the herbs exhibit that low antioxidant activity (below 45% at 1.0 mg/ml)and low anti-inflammatory activity (below 60% at 1.0 mg/ml), and group C stand for the herbs which possess high antioxidant activity (over 45% at 1.0 mg/ml) and high anti-inflammatoryactivity (over 60% at 1.0 mg/ml). Group A contains 2 kinds of agricultural by-products including PM and CM, and 6 kinds ofmedicinal herbs such as, RNN, CC, RO, MP, CLand LO. Group B includes GMas an

agricultural by-product and 6 kinds of medicinal herbs such as, BI, BB, AT, AG, OB and AS. Finally, group C involves two medicinal herbs such as, NN and CA(Fig. 1).Therefore, we suggest NN and CA which possess strong anti-inflammatory and antioxidant activity for the potential feed resources to produce thefunctional livestock products.

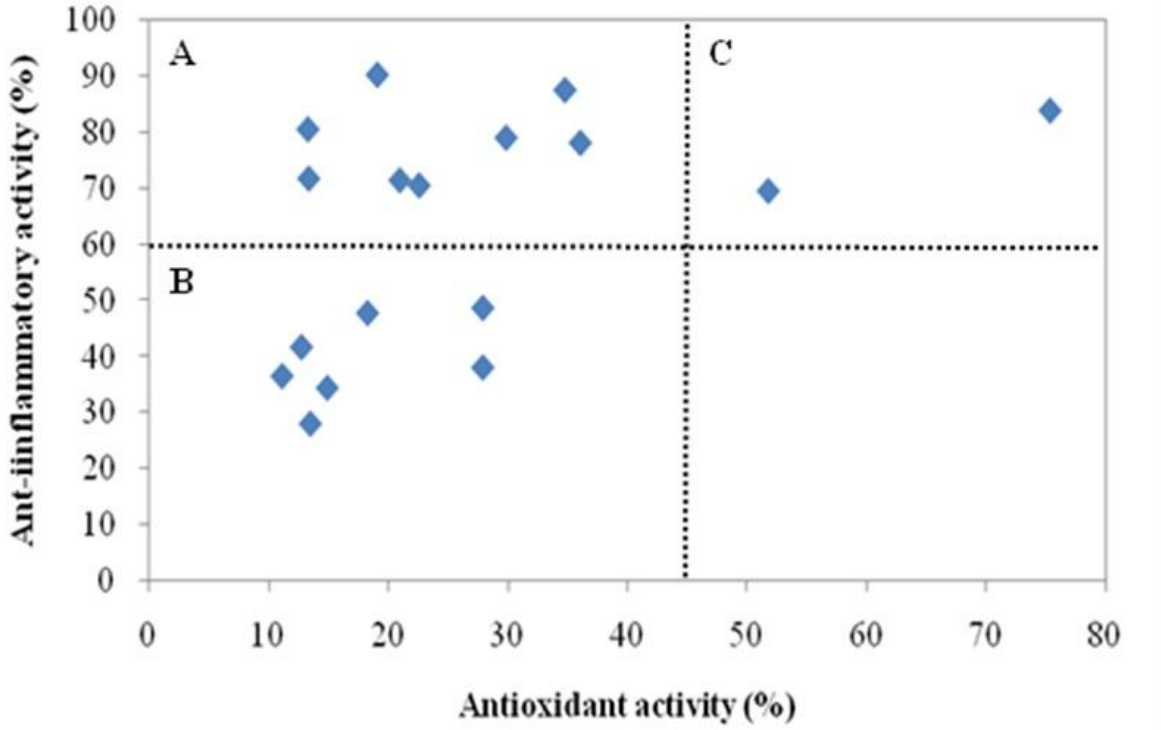

Fig. 1:The relationship of antioxidant and anti-inflammatory activities in the agricultural by-products and medicinal herbs.

Group A, the herbs have low antioxidant activity (below 45% at 1.0 mg/ml) and high anti-inflammatory activity (over 60% at 1.0 mg/ml). Group B, the herbs have low antioxidant activity (below 45% at 1.0 mg/ml) and low anti-inflammatory activity (below 60% at 1.0 mg/ml). Group C, the herbs have high antioxidant activity (over 45% at 1.0 mg/ml) and high anti-inflammatory activity (over 60% at 1.0 mg/ml).

Effect of the medicinal herbs on IFN-γ-induced iNOS and COX expression

In the present study, we also examined the effect of the medicinal herbs on IFN-γ-induced iNOS and COX expression in RAW264.7 cells. We confirmed that iNOS and COX-2 protein expression was increased by IFN-γ-stimulation. On the contrary, co-treatment of the agricultural by-products and medicinal herb extracts and IFN-γ significantly suppressed iNOS and COX-2 protein expression (Fig. 2). These results indicate that the agricultural by-products and medicinal herbs have the potential effects to inhibit pro-inflammatory mediators.NO is a major product and its production is controlled by the nitric oxide synthases (NOS) includingiNOS, eNOS and nNOS. Most importantly, iNOS is highly expressed in macrophages; its activation leads to organ destruction in some inflammatory and autoimmune diseases. Prostaglandin E2 (PGE_2) is another important inflammatory mediator and is produced from arachidonic acid metabolites by the catalysis of cyclooxygenase-2 (COX-2) [4, 17]. During inflammation, macrophages play a central role in managing many different immunopathological phenomena, including the overproduction of pro-inflammatory cytokines and inflammatory mediators such as IL-1ß, IL-6, NO, iNOS, COX-2

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and TNF-α. Indeed, a number of inflammatory stimuli and pro-inflammatory cytokines, such as LPS and IFN-γ activate immune cells to up-regulate such inflammatory states. Therefore, we investigated whether the suppression of NO production was due to the down-regulation of iNOS and COX-2 expression. RAW264.7 cells were treated with 100 μg/ml of each medicinal herb extracts for 4 h, followed by IFN-γ stimulation for 20 h. iNOS and COX-2 protein expression was increased by IFN-γ-stimulation. However, co-treatment of theagricultural by-products andmedicinal herb extracts and IFN-γsignificantly suppressed iNOS and COX-2 protein expression (Fig. 2). These results indicate that the herbs have the potential to inhibit pro-inflammatory mediators.

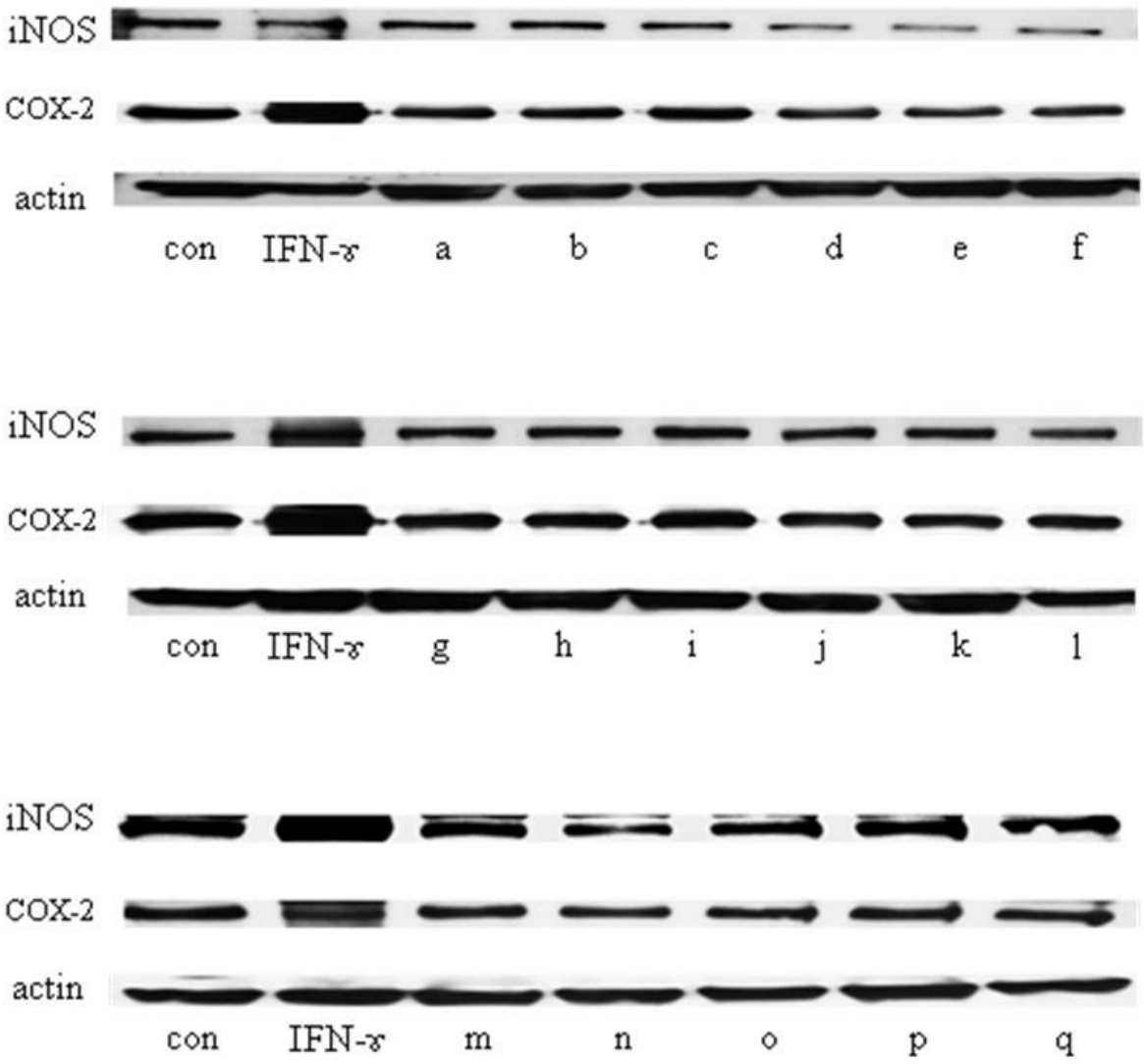

Fig. 2: Effect of the medicinal herbs on IFN-γ-inducediNOS and COX expression.

Total cell lysates (30 μg) were separated on 10% SDS–PAGE. iNOS, COX-2 and *β*-actin were detected by western blotting. RAW264.7 cells were incubated with or without IFN-γ and each herb extracts. a,*Chrysanthemum zawadskii var. latilobum*(CL); b, *Rosmarinusofficinalis*(RO); c, *Lavandulaofficinalis*(LO); d, *Cymbopogon citrates*(CC); e, *Menthapiperita*(MP); f, *Ocimumbasilicum*(OB); g, *Capsicum annuum*(CA); h, *Allium tuberosum*(AT); i, *Brassica oleracea var. italic*(BI); j, *Brassica oleracea var. botrytis*(BB); k, *Apiumgraveolens*(AG); l, *Allium sativum*(AS); m, *Nelumbonucifera*(NN); n, the root of *Nelumbonucifera*(RNN); o, *Panax ginseng* marc(PM); p, *Ginseng radix rubra* marc(GM); q, *Camellia sinensis* marc(CM).Fig. 2

Plant materials, such as leaves, seeds, vegetables, fruits, hulls, wood, bark, and roots, have been measured as potential sources of antioxidant compounds[22, 23, 24]. Especially, phenolic compounds are widely distributed in plants, which have gained much attention, due to their antioxidant activities and free radical-scavenging abilities, which potentially have beneficial implications for human health [7]. Flavonoids and other polyphenols possess, anti-allergic, anti-platelet, anti-ischemic, and anti-inflammatory activities, among others, and most of these effects are believed to be due to the antioxidant capacity. Therefore, we measured the contents of phenolic compounds however there was no relationship between the biological activity and the amounts (data not shown). Similar with our result, Pereira et al.[19] reported that the free radical scavenger activity of plant extracts from *M. officinalis*, *C. citratus* and *M. recutita* were not related with phenolic contents. Taken together, this study proposes that agricultural by-products and medicinal herbs possessing both antioxidant and anti-inflammatory activities could bevaluable source of natural antioxidantsfor producing the potential functional livestock products. Also, our results may guide people to understand biological activities of theagricultural by-products and herbs, and help to develop functional feed for production of safer and healthier animal products.

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