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In-vitro and in-vivo anti-inflammatory effect of oxyresveratrol from *Morus alba* L.

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Abstract

The antioxidative effects of mulberroside A and oxyresveratrol obtained from Mori Cortex were examined. Mulberroside A and oxyresveratrol showed an inhibitory effect against $FeSO_4$/H_2O_2-induced lipid peroxidation in rat microsomes and a scavenging effect on 1,1-diphenyl-2-picrylhydrazyl radical. The anti-inflammatory effects of mulberroside A and oxyresveratrol using the carrageenin-induced model of inflammation were investigated in rats. Mulberroside A and oxyresveratrol significantly reduced paw edema. To investigate the mechanism of the anti-inflammatory action of these compounds, we examined the effects of oxyresveratrol on lipopolysaccharide (LPS)-induced responses in murine macrophage cell line RAW 264.7. Exposure of LPS-stimulated cells to oxyresveratrol inhibited nitrite accumulation in the culture medium. Oxyresveratrol also inhibited the LPS-stimulated increase of inducible nitric oxide synthase (iNOS) expression in a concentration-dependent manner; however, it had little effect on iNOS enzyme activity, suggesting that the inhibitory activity of oxyresveratrol is mainly due to the inhibition of iNOS expression rather than iNOS enzyme activity. Oxyresveratrol significantly inhibited LPS-evoked nuclear translocation of NF-κB and cyclooxygenase-2 (COX-2) activity in RAW 264.7 cells. The results suggest that the anti-inflammatory properties of oxyresveratrol might be correlated with inhibition of the iNOS expression through down-regulation of NF-κB binding activity and significant inhibition of COX-2 activity.

Introduction

Mori Cortex is a dried root bark of *Morus alba* L. (Moraceae), and has been widely used as an antitussive, antiphlogistic and diuretic agent in Korea. However, there has been no experimental evidence for the anti-inflammatory effect of Mori Cortex, and the active principle for the effect has still to be determined.

Mulberroside A is one of the components of Mori Cortex, and it has been suggested that it expresses its pharmacological effects after being converted to oxyresveratrol (2,3′,4,5′-tetrahydroxystilbene) in the body (Qui et al 1996; Figure 1). However, very little information is available on the physiological activity of mulberroside A and oxyresveratrol except for the inhibitory effects of oxyresveratrol on tyrosinase activity (Kim et al 2002) and the histamine release activity from rat mast cells (Tsuruga et al 1991). Oxyresveratrol possesses structural similarities with resveratrol (2,3′,4-trihydroxystilbene), a representative of hydroxystilbene. Resveratrol is well known for its action as an antioxidant and antimutagen. It also mediates anti-inflammatory effects and inhibits cyclooxygenase activity (Jang et al 1997; Surh et al 2001; Dong 2003). In this study, we examined the anti-inflammatory effects of mulberroside A and oxyresveratrol as the active principles of Mori Cortex by using the carrageenin-induced edema model in rats. The effects of oxyresveratrol on lipopolysaccharide (LPS)-induced response in murine macrophage cell line RAW 264.7 were also investigated to clarify the mechanism of the anti-inflammatory activity of these compounds.

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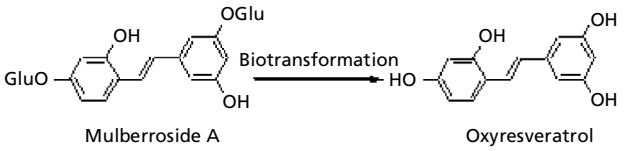

Figure 1 Structure of mulberroside A and oxyresveratrol.

Materials and Methods

Materials and animals

Mulberroside A was isolated from the water extract of Mori Cortex and oxyresveratrol was obtained by the enzymatic hydrolysis of mulberroside A with β-glucosidase (Hirakura et al 1986). Male Sprague–Dawley (SD) rats, 6 weeks of age and weighing 180–200 g, were obtained from Dae Han Laboratory Animal Research Center Co., Ltd (Korea) and maintained under a 12-h light/dark cycle in a temperature- and humidity-controlled room. Animal care and all experimental procedures were conducted in accordance with the Guide for Animal Experiments edited by the Korean Academy of Medical Sciences.

Inhibitory effect on lipid peroxidation in rat liver microsomes and radical scavenging effect on 1,1-diphenyl-2-picrylhydrazyl (DPPH)

Lipid peroxidation in rat liver microsomes induced by the Fenton reaction, comprising 0.1 mM $FeSO_4$, 3 mM H_2O_2, various concentrations of the tested substances and liver microsomes (1.9 mg protein mL^{-1}), was measured by the method of Buege and Aust (1978) with some modifications. The reaction was started by the addition of $FeSO_4$ and H_2O_2 and then incubated at 37 °C for 10 min. The reaction was stopped by mixing with 3 mL of a stock solution of 15% (w/v) trichloroacetic acid, 0.375% (w/v) thiobarbituric acid, 0.125 M hydrochloric acid, and 0.6 mM butylhydroxytoluene (BHT). The combination of reaction mixture and stock solution was heated for 30 min in a boiling water bath. After cooling, the flocculent precipitate was removed by centrifugation at 1250 *g* for 20 min. The absorbance of the supernatant was determined at 532 nm and the malonedialdehyde (MDA) concentration was calculated using 1,1,3,3-tetraethoxypropane as a standard. Protein concentrations were determined by the Lowry method (Lowry et al 1951) using bovine serum albumin as a standard.

The reaction mixture used to test the radical scavenging effect on DPPH consisted of 0.5 mL of 60 μM ethanolic solution of DPPH and 0.5 mL of sample water solution. After allowing the mixture to stand at room temperature for 30 min, the absorbance of the remaining DPPH was determined at 520 nm. The scavenging activity of each sample was expressed as a percentage of the decrease in absorbance of DPPH against that of control DPPH solution (Hamada et al 1993).

Carrageenin-induced hind-paw edema in rats

Animals were fasted for 24 h prior to experiments, but were supplied with water ad libitum. Carrageenin (0.05 mL, 1% w/v) solution in 0.9% saline was subcutaneously injected into the right hind-paw 30 min after the tested substances were given to rats orally. The control group received the vehicle. The volume of the hind-paw was measured with a plethysmometer (No. 7140, Ugo Basile) before and at 2, 3 and 5 h after carrageenin injection. The results were expressed as the percentage of hind-paw swelling as compared with the initial hind-paw volume. Indometacin was used as a standard drug.

Cell culture

RAW 264.7, a mouse macrophage cell line, was obtained from the Korean Cell Line Bank (Seoul). Cells were cultured in Dulbecco's Modified Eagle Medium supplemented with 10% heat-inactivated fetal bovine serum (GIBCO, BRL), 2% glutamine, 100 U mL^{-1} penicillin, 100 μg mL^{-1} streptomycin, and 0.25 μg mL^{-1} amphotericin B in a humidified atmosphere of 5% CO_2, 95% air. Treatment with oxyresveratrol and/or LPS (100 ng mL^{-1}) was carried out under serum-free conditions. Cell viability was examined using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay (Moon et al 1998).

Effect on inducible nitric oxide synthase (iNOS) enzyme activity

The nitrite concentration in the culture medium was measured as an indicator of nitric oxide (NO) production according to the Griess reaction (Green et al 1982). One hundred microlitres of each supernatant was mixed with the same volume of Griess reagent (1% sulfanilamide in 5% phosphoric acid and 0.1% naphthylethylenediamine dihydrochloride in water) and the absorbance of the mixture at 550 nm was determined with a microplate reader (Packard Instrument Co., USA).

The cells were stimulated with LPS (100 ng mL^{-1}) to induce iNOS for 18 h and washed with fresh medium. Various concentrations of oxyresveratrol were added and incubated for a further 18 h (Huang et al 2001). The supernatants were removed and assayed for nitrite as described above.

Immunological detection of iNOS

Following stimulation, cells were washed twice with ice-cold phosphate-buffered saline and then lysed in a buffer containing 0.5% Nonidet P40 (NP40), 10 mM HEPES, 100 mM NaCl, 100 μM phenylmethylsulfonyl fluoride, 5 μg mL^{-1} aprotinin and 10 μg mL^{-1} leupeptin. The supernatant was collected and protein concentrations were determined using a protein-assay kit (Sigma). Equal amounts of total cellular proteins (30 μg) for each sample were boiled and separated on 6% SDS-polyacrylamide minigels and transferred to polyvinylidene difluoride membrane (Amersham). Non-specific binding to the membrane was blocked by 5% non-fat

milk-blocking buffer containing 10 mM Tris (pH 7.5), 100 mM NaCl and 0.1% Tween 20. The membrane was then incubated overnight at 4 °C with anti-iNOS polyclonal antibodies (Santa Cruz Biotechnology, Santa Cruz, CA). β-actin was used as a control, in company with the immunoblot of iNOS expression. The membrane was subsequently probed with anti-rabbit IgG antibody conjugated with horseradish peroxidase (Santa Cruz Biotechnology) and visualized using an enhanced chemiluminescence detection system (ECL, Amersham).

Electrophoretic mobility shift assay

The electrophoretic mobility shift assay method was used to characterize the binding activities of NF-κB in nuclear extracts (Kerr 1995). The preparation of nuclear extracts was based on previous methods (Hattori et al 1990), and the concentration of total protein in samples was measured with Sigma protein assay reagent kit containing bicinchoninc acid. NF-κB oligonucleotide was 5′-GAGAGGCAAGGG GATTCCCTTAGTTAGGA-3′. Protein–DNA binding assays were performed with 10 μg of nuclear protein. To minimize salt on binding, the concentration of salt was adjusted to the same level in all samples. Nonspecific binding was blocked by using 1 μg of poly(dI-dC). The binding medium contained 5% glycerol, 1 mM $MgCl_2$, 50 mM NaCl, 0.5 mM EDTA, 2 mM DTT, 1% NP40 and 10 mM Tris/HCl, pH 7.5. In each reaction, 20 000 cpm of radiolabelled probe was included. Samples were incubated at room temperature for 20 min, and the nuclear protein–^{32}P-labelled oligonucleotide complex was separated from free ^{32}P-labelled oligonucleotide by electrophoresis through a 5% native polyacrylamide gel in a running buffer containing 50 mM Tris, pH 8.0, 45 mM borate and 0.5 mM EDTA. Separation was achieved, and the gel was vacuum dried for autoradiography and exposed to Fuji X-ray film for 1–2 days at −75 °C.

Measurement of prostaglandin E_2 (PGE_2) production

The culture medium of control and treated cells was collected. The level of PGE_2 released into culture medium was quantified using a specific enzyme immunoassay according to the manufacturer's instructions (Amersham).

Statistical analysis

All values were expressed as the mean ± s.d. Significant differences between the groups were statistically analysed using a one-way ANOVA, followed by a non-parametric post-hoc test (LSD). A P value of 0.05 or less was considered statistically significant.

Results and Discussion

Antioxidative activities of mulberroside A and oxyresveratrol

There is considerable evidence from both in-vitro and in-vivo studies that oxygen-derived radicals play a role in acute inflammation (Conner & Grisham 1996). In this study, the antioxidative activities of mulberroside A and oxyresveratrol were investigated by the examination of the inhibitory effect against $FeSO_4/H_2O_2$-induced lipid peroxidation in rat liver microsomes and the DPPH radical scavenging effect (Table 1). As positive controls, BHT and resveratrol, which are well-known antioxidants, were also tested. The potency order in inhibiting lipid peroxidation induced by $FeSO_4/H_2O_2$ was BHT > oxyresveratrol > resveratrol > mulberroside A, and the rank in scavenging effect on DPPH radicals was oxyresveratrol > resveratrol > BHT > mulberroside A. Oxyresveratrol exhibited more potent antioxidative activity than resveratrol, whereas mulberroside A showed a less potent effect compared to other substances tested.

Inhibitory effects of mulberroside A and oxyresveratrol on carrageenin-induced paw edema in rats

We examined the anti-inflammatory effect of mulberroside A and oxyresveratrol using the carrageenin-induced edema model (Table 2). Generally, indometacin is used as a positive control for the anti-inflammatory effect at a dose of 10 mg kg^{-1} in rats. In this experiment, we decided to test the anti-inflammatory effect of oxyresveratrol with the same amount, 10 mg kg^{-1} (not equi-molar), and a smaller amount, 7.5 mg kg^{-1}. The corresponding equi-molar doses of mulberroside A are 23.5 or 17.6 mg kg^{-1}, respectively, according to the molecular weights of oxyresveratrol (m.w. 244) and mulberroside A (m.w. 568). However, we injected mulberroside A at about twice the equi-molar dose, i.e. 50 or 37.5 mg kg^{-1} because Qui et al (1996) suggested that orally administered mulberroside A was metabolized in the liver or digestive tract to oxyresveratrol, and about 50% of its metabolites were absorbed into the circulating blood. Mulberroside A and

Table 1 Antioxidative activities of mulberroside A and oxyresveratrol against the lipid peroxidation of rat liver microsomes induced by $FeSO_4$ and H_2O_2, and against DPPH radical.

Substances	IC_{50} (μM)	
	Lipid peroxidation[a]	DPPH radical[b]
Mulberroside A	78.4 ± 3.2	91.3 ± 8.3
Oxyresveratrol	3.6 ± 0.0	15.1 ± 2.3
Resveratrol	6.1 ± 0.1	21.7 ± 2.9
BHT	1.0 ± 0.0	39.8 ± 1.6

[a]The reaction mixture (1.0 mL) was composed of rat liver microsomes (1.9 mg protein), 0.1 mM $FeSO_4$, 3 mM H_2O_2, and various concentrations of substances. After incubation at 37 °C for 10 min, the amount of MDA was measured by the method of Buege and Aust (1978).[b] The reaction mixture consisted of 0.5 mL of 60 μM ethanolic solution of DPPH and 0.5 mL of various concentrations of sample solution. After allowing the mixture to stand at room temperature for 30 min, the absorbance of the remaining DPPH was determined at 520 nm.

Table 2 Effects of mulberroside A and oxyresveratrol on the carrageenin-induced paw edema in rats.

Substances	Animals	Dose ($mg\,kg^{-1}$)	% Increased volume of paw[a] (% anti-inflammatory effect)[b]		
			2 h	3 h	5 h
Control	8		36.8 ± 9.4	43.1 ± 4.5	23.6 ± 7.6
Mulberroside A	7	37.5	28.3 ± 6.9 (23.2)*	26.9 ± 10.5 (24.1)**	13.9 ± 9.7 (39.6)**
	8	50.0	18.6 ± 8.4 (49.5)***	18.7 ± 7.9 (56.6)***	9.2 ± 6.9 (61.1)***
Oxyresveratrol	6	7.5	18.5 ± 9.8 (49.9)***	26.9 ± 10.5 (37.5)***	13.4 ± 9.7 (43.4)**
	7	10.0	13.7 ± 4.6 (62.9)***	15.8 ± 4.5 (63.3)***	8.0 ± 6.6 (66.1)***
Indometacin	5	7.5	10.9 ± 5.4 (70.4)***	17.3 ± 5.3 (83.7)***	8.6 ± 3.7 (63.6)***
	7	10.0	6.9 ± 4.5 (81.3)***	7.0 ± 3.1 (59.9)***	1.8 ± 2.7 (92.3)***

All values are means ± s.d. [a]Increased volume of paw (%) was obtained by comparing the paw volume of rat before the inflammation with that at 2, 3 and 5 h after injection of carrageenin. [b]Anti-inflammatory effect was calculated by the following equation: anti-inflammatory activity (%) = (1 − A/B) × 100, where A represents the percentage difference in paw volume at the time indicated after substance was administrated to the rats, and B represents the percentage of volume in the control group. *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$ indicate statistically significant differences from the control group.

oxyresveratrol inhibited the edema induced by carrageenin in a dose-dependent manner. After 3 h, mulberroside A at doses of 37.5 and $50\,mg\,kg^{-1}$ decreased the paw edema induced by carrageenin at rates of 24.1 and 56.6%, respectively. Oxyresveratrol at doses of 7.5 and $10\,mg\,kg^{-1}$ decreased the edema by 37.5 and 63.3%, respectively. Although the anti-inflammatory effects of mulberroside A and oxyresveratrol were less potent than that of indometacin, these results demonstrate the potential of mulberroside A and oxyresveratrol as the active components of Mori Cortex.

The anti-inflammatory effect of oxyresveratrol was much stronger than that of mulberroside A and the edema-suppressing activity of oxyresveratrol 3 h after injection was similar to that of five times the amount of mulberroside A (10 mg oxyresveratrol versus 50 mg mulberroside A, and 7.5 mg oxyresveratrol versus 37.5 mg mulberroside A). These results were consistent with the findings of Qui et al (1996). Comparison of the data obtained at 2, 3 and 5 h revealed a more delayed effect of mulberroside A with respect to the corresponding biotransformed oxyresveratrol, suggesting a typical pro-drug behaviour of mulberroside A and confirming Qui's hypothesis.

Inhibition of NO production and protein levels by oxyresveratrol in LPS-stimulated RAW 264.7 cells

To investigate the mechanism of action of mulberroside A and oxyresveratrol as anti-inflammatory agents, the effects of oxyresveratrol, which is supposed to be the active form of mulberroside A in the body, on the LPS-induced response in murine macrophage cell line RAW 264.7 were investigated.

NOSs play a major role in regulating vascular tone, neurotransmission and other homeostatic mechanisms. High levels of NO have been described in a variety of pathophysiological processes, including inflammation.

Table 3 Effect of oxyresveratrol on LPS-induced nitrite and PGE_2 production in RAW 264.7 cells.

Treatment	Nitrite (% inhibition)	PGE_2 (% inhibition)
Cell only	0.9 ± 0.0	0.5 ± 0.1
LPS ($100\,ng\,mL^{-1}$)	22.3 ± 0.8	30.4 ± 1.2
+ Oxyresveratrol 10 μM	20.7 ± 0.1(7.8)	22.5 ± 1.9(26.6)***
+ Oxyresveratrol 50 μM	12.2 ± 1.7(47.2)***	2.8 ± 0.1(89.5)***
+ Oxyresveratrol 100 μM	6.2 ± 0.4(75.2)***	0.2 ± 0.1(100)***

The cells were treated with $100\,ng\,mL^{-1}$ of LPS only or LPS plus different concentrations of oxyresveratrol for 18 h. At the end of incubation, 100 μL of the medium was removed to measure nitrite production or the level of PGE_2 released into culture medium was quantified using a specific enzyme immunoassay according to the manufacturer's instructions (Amersham). Control values were obtained in the absence of LPS or oxyresveratrol. The units of NO and PGE_2 are μM and $ng\,mL^{-1}$, respectively. Data were derived from three independent experiments and expressed as means ± s.d. ***$P < 0.001$ indicates statistically significant differences from the LPS-treated group.

iNOS, which is induced in response to interferon-γ (IFN-γ), LPS and a variety of pro-inflammatory cytokines, is responsible for the overproduction of NO in inflammation (Liang et al 1999).

In RAW 264.7 cells, LPS stimulation could induce the iNOS transcription that follows NO production. The cells were stimulated with LPS ($100\,ng\,mL^{-1}$) for 18 h to induce NO production. As shown in Table 3, LPS induced a significant increase of nitrite production and this effect was concentration dependently suppressed by oxyresveratrol with an IC_{50} value of 46.8 μM.

On the premise that this effect might be mediated due to inhibition of iNOS induction, the effect of oxyresveratrol

on iNOS protein induction after LPS stimulation was examined by Western blot analysis. As shown in Figure 2, the cells expressed barely detectable levels of iNOS protein under normal conditions; however, iNOS expression was markedly increased after 18 h in response to LPS (100 ng mL^{-1}). The administration of oxyresveratrol caused a concentration-dependent decrease in LPS-stimulated iNOS expression.

However, the inhibition of iNOS enzyme activity also could reduce the subsequent NO production. Therefore the effect of oxyresveratrol on iNOS enzyme activity was also examined. For this purpose, cells were stimulated with LPS (100 ng mL^{-1}) for 18 h, which resulted in a profound increase in iNOS protein level, and then oxyresveratrol was added to the cells with refreshed medium. After an 18 h incubation period, the medium nitrite was assayed to examine the effect of oxyresveratrol on iNOS enzyme activity. The results showed that oxyresveratrol was unable to effectively suppress this iNOS-activated nitrite accumulation, and only produced a slight inhibition of iNOS activity (Table 4). The extent of inhibition by oxyresveratrol on iNOS enzyme activity (IC_{50}, 3.1 mM) was not parallel with that of total nitrite accumulation (IC_{50}, 46.8 μM), suggesting that the inhibitory action of oxyresveratrol is due mainly to the inhibition of iNOS expression rather than of iNOS enzyme activity. Furthermore, the cytotoxic effect of oxyresveratrol was also examined using the MTT assay method, but no significant decrease in cell viability was observed when a high concentration of oxyresveratrol (100 μM) was used (data not shown).

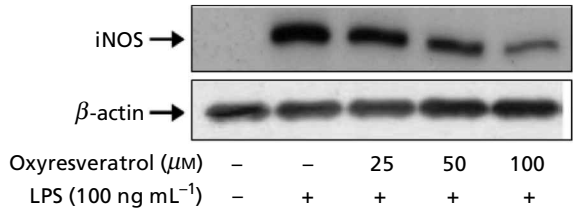

Figure 2 Western blot analysis of the inhibition of LPS-induced iNOS protein expression in RAW 264.7 cells by oxyresveratrol. The cells were treated with LPS (100 ng mL^{-1}) and various concentrations of oxyresveratrol for 18 h. Equal amounts of total proteins (30 μg lane^{-1}) were subjected to 6% SDS-PAGE, and expression of iNOS protein was detected by Western blotting using antibody for iNOS.

Table 4 Effect of oxyresveratrol on iNOS activity in LPS-activated RAW 264.7 cells.

Treatment	Nitrite (μM)	Inhibition (%)
Cell only	2.2 ± 0.1	
LPS (100 ng mL^{-1})	35.0 ± 0.7	
+ Oxyresveratrol 10 μM	34.8 ± 0.8	0.1 ± 2.4
+ Oxyresveratrol 50 μM	29.3 ± 1.6***	17.4 ± 4.9
+ Oxyresveratrol 100 μM	28.4 ± 1.5***	20.1 ± 4.6

The cells were stimulated with LPS (100 ng mL^{-1}) to induce iNOS for 18 h and washed with fresh medium. Various concentrations of oxyresveratrol were then added and incubated for a further 18 h. At the end of incubation, 100 μL of the medium was removed to measure nitrite production. Data were derived from three independent experiments and expressed as means ± s.d. ***$P < 0.01$ indicates statistically significant differences from the LPS-treated group.

Effects of oxyresveratrol on LPS-induced NF-κB translocation

In macrophages, LPS activates the transcription factor NF-κB, which leads to induction of expression of many immediate early genes, such as iNOS (Kim et al 1997). To examine the mechanism by which iNOS expression was inhibited, the effect of oxyresveratrol in LPS-induced NF-κB nuclear translocation was investigated in RAW 264.7 cells. Cells were pretreated with oxyresveratrol (5–100 μM) for 30 min, and then LPS (100 ng mL^{-1}) was added to the cells for another 30 min. As shown in Figure 3, the basal level of nuclear NF-κB binding activity was hardly detected in unstimulated cells. However, the stimulation with LPS resulted in a profound increase in the nuclear translocation. Consequently, oxyresveratrol showed significant inhibition of the LPS-induced NF-κB binding activity at low concentrations (5 μM), although it could not abolish it completely at high concentrations of

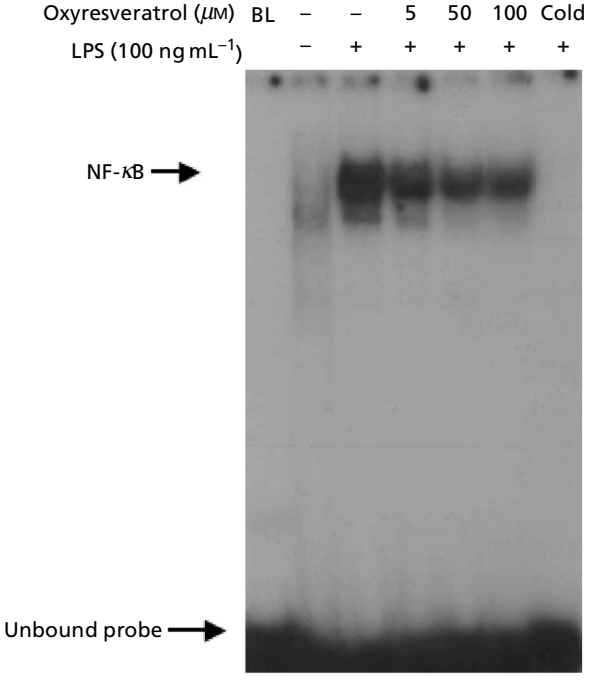

Figure 3 Effect of oxyresveratrol on LPS-induced NF-κB nuclear translocation in RAW 264.7 cells. Cells were pretreated with various concentrations of oxyresveratrol for 30 min, then LPS (100 ng mL^{-1}) was added to the cells for another 30 min. Five micrograms of nuclear extract was used for each reaction.

oxyresveratrol (100 μM). This result suggests that oxyresveratrol inhibited the induction of iNOS in the LPS-stimulated macrophage cell line through an inhibition of NF-κB nuclear translocation.

Inhibition of PGE_2 generation by oxyresveratrol in LPS-stimulated RAW 264.7 cells

Prostaglandins, the products generated by cyclooxygenase (COX) from arachidonic acid, are important mediators in the inflammatory process (Lee et al 1992). In this study, we investigated whether oxyresveratrol may also influence the generation of PGE_2, a product of the COX-2 enzyme, in LPS-activated RAW 264.7 cells. As shown in Table 3, stimulation with LPS (100 ng mL^{-1}) for 18 h resulted in a significant accumulation of PGE_2 in the medium, and this effect was concentration dependently suppressed by oxyresveratrol with an IC_{50} value of 19.1 μM.

Conclusions

Mori Cortex has been widely used as an anti-inflammatory agent in Korea. However, no experimental evidence on the anti-inflammatory effect of Mori Cortex has been obtained, and the active principle for the effect has remained to be determined. In this study, we have demonstrated that mulberroside A and oxyresveratrol exhibit an in-vivo anti-inflammatory effect on carrageenin-induced paw edema in rats, suggesting these compounds as the active components of Mori Cortex.

To investigate the mechanism of the action, we examined the effect of oxyresveratrol on NO production and PGE_2 biosynthesis, which have been implicated in the process of inflammation. Oxyresveratrol significantly inhibited the production of nitrite, iNOS expression and NF-κB activation in the LPS-activated RAW 264.7 macrophage. Furthermore, oxyresveratrol reduced PGE_2 reduction in the LPS-stimulated macrophage. These results suggest that the anti-inflammatory properties of oxyresveratrol might be correlated to inhibition of the iNOS expression through down-regulation of NF-κB binding activity and significant inhibition of PGE_2 production.

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