Monoacetylcurcumin strongly regulates inflammatory responses through inhibition of NF-κB activation

MASAYUKI NISHIDA1,3, SHIN NISHIUMI1,2, YOSHIYUKI MIZUSHINA3,4, YOSHIKI FUJISHIMA1, KOJI YAMAMOTO1, ATSUHIRO MASUDA1,5, SHIGETO MIZUNO5, TSUYOSHI FUJITA1, YOSHINORI MORITA1, HIROMU KUTSUMI1, HIROMI YOSHIDA3,4, TAKESHI AZUMA1 and MASARU YOSHIDA1,2

1Division of Gastroenterology, Department of Internal Medicine, 2The Integrated Center for Mass Spectrometry, Graduate School of Medicine, Kobe University, 7-5-1 Chu-o-ku, Kusunoki-Cho, Kobe, Hyogo 650-0017; 3Laboratory of Food and Nutritional Sciences, Department of Nutritional Science, 4Cooperative Research Center of Life Sciences, Kobe-Gakuin University, Nishi-ku, Kobe, Hyogo 651-2180; 5Medical Pharmaceutics, Kobe Pharmaceutical University, Higashinada-ku, Kobe, Hyogo 658-8558, Japan

Received November 26, 2009; Accepted January 12, 2010

DOI: 10.3892/ijmm_00000402

Abstract. Curcumin, a component of turmeric (Curcuma longa), is known to exert a variety of biological functions including anti-inflammatory activity. We examined the inhibitory effects of chemically synthesized derivatives of curcumin against inflammatory responses and compared them with those of curcumin, in order to find derivatives with stronger effects than curcumin. In a cell culture system using the mouse macrophage cell line RAW264.7, monoacetylcurcumin strongly inhibited IκB phosphorylation, nuclear factor (NF)-κB activation and tumor necrosis factor (TNF)-α production induced by lipopolysaccharide (LPS). In addition, oral administration of monoacetylcurcumin to mice led to greater suppression of TNF-α production after LPS stimulation than the administration of curcumin or tetrahydrocurcumin in vivo. Monoacetylcurcumin also inhibited the LPS-induced NF-κB activation in the liver. Collectively, monoacetylcurcumin is a potential chemopreventive agent for treating inflammatory responses more effectively than curcumin.

Introduction

Curcumin (diferuloylmethane; 1,7-bis(4-hydroxy-3-methoxy-phenyl)-1-6-heptadine-3,5-dione) is one of the biologically active compounds found in the Indian spice turmeric (Curcuma longa). It belongs to a family called curcuminoids and usually comprises approximately 3% of turmeric powder, which is commonly used as a preservative in foods and a yellow pigment in textiles. Presently, curcumin is well known as an anti-oxidant agent, and the pharmacological potential of curcumin is under investigation (1).

Previous studies have found that some naturally occurring compounds including curcumin are potential therapeutics for treating nuclear factor (NF)-κB-dependent inflammatory responses (2). The activation of NF-κB is the rate-limiting step for various inflammatory responses (3). The five members of the mammalian NF-κB family, namely p65 (RelA), RelB, c-Rel, p50/p105 (NF-κB1) and p52/p100 (NF-κB2), exist in unstimulated cells as homodimers or heterodimers bound to IκB family proteins (4). The binding of NF-κB to IκB prevents NF-κB from translocating to the nucleus, thereby maintaining NF-κB in an inactive state. NF-κB proteins are characterized by the presence of a conserved 300-amino acid Rel homology domain located in the N terminus of the protein, and the domain is responsible for dimerization with NF-κB, interaction with IκB, and binding to DNA (4). The translocated NF-κB works as transcription factors and regulate the expression of various genes that encode proinflammatory cytokines such as tumor necrosis factor (TNF)-α and IL-12, which have been shown to play important roles in sustained inflammatory responses (5-7). In fact, it was found that curcumin ameliorates trinitrobenzene sulfonic acid (TNBS)-induced colitis in mice (8), which is a mouse model of inflammatory bowel disease, and curcumin suppressed the CD4+ T-cell infiltration and NF-κB activation in colonic mucosa (8).

After absorption into the human body, curcumin undergoes metabolic conversion to its sulfate, glucuronide, and sulfated-glucuronide conjugate (9). In the liver, curcumin is converted to hexahydrocurcumin, tetrahydrocurcumin and hexahydrocurcuminol through endogenous reductase systems (10). Tetrahydrocurcumin has been demonstrated to be the major curcumin metabolite in vivo (11) and is an active metabolite...
of curcumin. Tetrahydrocurcumin has also been widely studied due to its potential anti-oxidant, anti-inflammatory and anticarcinogenic activities and its ability to modulate multidrug-resistant proteins (12-14). Therefore, there is a possibility that tetrahydrocurcumin plays a crucial role in the biological effects of curcumin in vivo. Thus, curcumin and tetrahydrocurcumin are potential anti-inflammatory agents.

Various curcumin derivatives, such as demethoxycurcumin, bisdemethoxycurcumin, turmerones and monoacetylcurcumin, have been chemically synthesized in the hope of discovering derivatives exhibiting a higher biological activity than curcumin (15). In our previous study, we found that curcumin selectively inhibits the activity of DNA polymerase \( \lambda \) in the 10 species of mammalian DNA polymerases tested (16). We also investigated the inhibition of DNA polymerase \( \lambda \) by 13 chemically synthesized derivatives of curcumin and found that monoacetylcurcumin was the strongest inhibitor of DNA polymerase \( \lambda \) among the curcumin derivatives and curcumin (17), suggesting that monoacetylcurcumin is a potent candidate for functional compounds. In this study, we investigated the inhibitory effects of monoacetylcurcumin on inflammatory responses in comparison with those of curcumin and tetrahydrocurcumin in vitro and in vivo. Monoacetylcurcumin suppressed NF-\( \kappa \)B activation induced by lipopolysaccharide (LPS) and TNF-\( \alpha \) in mouse macrophage RAW264.7 and human embryonic kidney HEK293 cells, respectively. Moreover, we also demonstrated that monoacetylcurcumin exerts inhibitory effects against TNF-\( \alpha \) production and NF-\( \kappa \)B activation in an LPS-induced acute inflammation animal model.

Materials and methods

Chemicals. Curcumin (Fig. 1A) and LPS were purchased from Sigma (St. Louis, MO). Monoacetylcurcumin (Fig. 1B) and tetrahydrocurcumin (Fig. 1C) were chemically synthesized from curcumin as described in reports by Takeuchi et al (17) and Sugiyama et al (18), respectively. The purity of the synthesized tetrahydrocurcumin and monoacetylcurcumin was >98% (data not shown). For Western blot analysis, anti-NF-\( \kappa \)B p65 antibody and horseradish peroxidase-conjugated anti-rabbit IgG antibody were obtained from Santa Cruz Biotechnology (Santa Cruz, CA) and Thermo Scientific (Kanagawa, Japan), respectively.

Cell culture. The human embryonic kidney cell line HEK293 and the murine macrophage cell line RAW264.7 were maintained in DMEM supplemented with 4.5 g glucose per liter plus 10% fetal calf serum, 5 mM L-glutamine, 50 units/ml penicillin and 50 units/ml streptomycin and were cultured in a humidified incubator with an atmosphere of 95% air and 5% CO2 at 37˚C.

Measurement of the TNF-\( \alpha \) secreted from RAW264.7 cells. RAW264.7 cells were seeded on a 12-well plate at 1x10\(^5\) cells/well and incubated for 24 h. The cells were pretreated with 10 or 50 \( \mu \)M curcumin, tetrahydrocurcumin or monoacetylcurcumin for 30 min and then stimulated with 100 ng/ml LPS. After 24 h, the cell culture medium was collected to measure the TNF-\( \alpha \) level. The concentration of TNF-\( \alpha \) in the culture medium was quantified using a commercially available ELISA development system (Bay Bioscience Co., Ltd., Kobe, Japan) according to the manufacturer’s protocol.

Cell treatment and preparation of nuclear and whole cellular proteins. RAW264.7 and HEK293 cells were pretreated with 50 \( \mu \)M curcumin, tetrahydrocurcumin or monoacetylcurcumin for 30 min followed by treatment with 100 ng/ml LPS for RAW264.7 cells and 20 ng/ml TNF-\( \alpha \) for HEK293 cells. After 30 min, the nuclear proteins and whole cell lysates were isolated from RAW264.7 cells and/or HEK293 cells as described in a previous report (19). The protein concentrations of the nuclear proteins and whole cell lysates were measured using BCA™ Protein Assay Kit (Pierce, Rockford, IL) according to the manufacturer’s protocol. Briefly, 25 \( \mu \)l of each sample or 2 mg/ml BSA solution as a standard was added to a 96-well microplate well, and then 200 \( \mu \)l of BCA Working Reagent was added to each well. This microplate was incubated at 37˚C for 30 min, and the protein concentration was determined by measurement of an absorbance at 575 nm. The nuclear proteins and whole cell lysates were subjected to Western blotting to evaluate the nuclear translocation of NF-\( \kappa \)B and phosphorylation of IkB.

Western blotting. The nuclear proteins (30-50 \( \mu \)g proteins) and whole cell lysates (50 \( \mu \)g proteins) were boiled in a quarter volume of sample buffer (1 M Tris-HCl, pH 7.5, 640 mM 2-mercaptoethanol, 0.2% bromphenol blue, 4% SDS and 20% glycerol) and then separated on 10% SDS-polyacrylamide gels. The proteins in the gels were transferred to a PVDF membrane. The membrane was blocked with 1% skimmed milk for NF-\( \kappa \)B p65 or 5% bovine serum albumin for phosphorylated IkB in TBS-T (10 mM Tris-HCl, 100 mM NaCl and 0.5% Tween-20) and probed with anti-NF-\( \kappa \)B p65 antibody (1:1000) or anti-phospho-IkB antibody (1:1000).
before being reacted with the horseradish peroxidase-conjugated secondary antibody. The protein-antibody complex was detected using ChemiLumiONE (Nacalai Tesque, Japan) and an Image Reader (LAS-3000 Imaging System, Fuji Photo Film). The intensity of each band was analyzed using ImageJ, which was developed at the National Institutes of Health.

**Determination of intracellular ROS.** Measurement of intracellular reactive oxygen species (ROS) was performed according to the method of a previous report (20). ROS generation in the cells was assessed using the probe 2,7-dichlorodihydrofluorescein (DCF) and 2',7'-dichlorofluorescein diacetate (DCFH-DA). The cells were treated with 4 μM DCFH-DA and curcumin, tetrahydrocurcumin or monoacetylcurcumin. After 30 min, the cells were treated with 4 μM DCFH-DA and 50 ng/ml TNF-α for 30 min in the presence or absence of curcumin, tetrahydrocurcumin or monoacetylcurcumin. The DCF fluorescence intensity of DCF was analyzed with a fluorescence reader (Thermo Scientific) using 485 nm excitation and 538 nm emission filters.

**Animal experiment.** All animal studies were performed according to the guidelines outlined in the ‘Care and Use of Laboratory Animals’ of Kobe-Gakuin University. The animals were anesthetized with pentobarbital before undergoing cervical dislocation. Male 8-week-old C57BL/6 mice that had been bred in-house with free access to food and water were used for all experiments. All of the mice were maintained under a 12-h light/dark cycle and housed at a room temperature of 25°C. The mice were orally administered 100 mg/kg body weight curcumin, tetrahydrocurcumin or monoacetylcurcumin dissolved in corn oil, respectively, or 200 μl of corn oil as a vehicle control. After 2 h, the mice were intraperitoneally injected with 250 μg/kg body weight (BW) LPS dissolved in PBS or 200 μl of PBS as a vehicle control. After 1 h, the mice were sacrificed, and their blood and liver were collected. The blood serum was separated by centrifugation at 15,000 x g for 10 min at 4°C. The TNF-α level in the serum was measured using ELISA. Nuclear proteins in the liver were prepared according to the method of a previous report (21), and the protein concentration was measured by BCA assay. The nuclear proteins were subjected to Western blotting to evaluate the nuclear translocation of NF-κB.

**Statistical analysis.** All data are expressed as means ± SE of at least three independent determinations for each experiment. Statistical significance was analyzed using the Student's t-test, and a level of probability of 0.05 was used as the criterion of significance.

**Results**

The inhibitory activity of curcumin and curcumin derivatives against inflammatory responses in cultured cells. First, the inhibitory activity of curcumin, tetrahydrocurcumin and monoacetylcurcumin against the LPS-induced TNF-α production in RAW264.7 cells was investigated to assess their anti-inflammatory activity (Fig. 2A). In RAW264.7 cells, cytotoxicity of curcumin, tetrahydrocurcumin and monoacetylcurcumin at 50 μM was not observed (data not shown). We found that 50 μM curcumin, tetrahydrocurcumin or monoacetylcurcumin significantly suppressed the 100 ng/ml LPS-stimulated TNF-α production, and the order of inhibitory activity was monoacetylcurcumin > curcumin >> tetrahydrocurcumin. At 10 μM, the significant suppressive effects of tetrahydrocurcumin and monoacetylcurcumin on TNF-α production were confirmed, although tetrahydrocurcumin did not exhibit a dose-dependent effect. Curcumin at 10 μM did not significantly inhibit the TNF-α production. The IC50 values of curcumin and monoacetylcurcumin were 29.8 and 23.4 μM, respectively; the IC50 value of tetrahydrocurcumin was not determined (Fig. 2B). NF-κB is known to be the rate-controlling factor for inflammatory responses. Therefore, the inhibitory effects of curcumin, tetrahydrocurcumin and monoacetylcurcumin on the TNF-α production were confirmed, although tetrahydrocurcumin did not block the nuclear translocation. It was found that stimulation with LPS results in the activation of Toll-like receptor 4 and the downstream IkB kinases (IKKs), which in turn phosphorylate IkB, the degradation of IkB and the translocation of NF-κB into the nucleus (22). Therefore, the suppressive effects of curcumin, tetrahydrocurcumin and monoacetylcurcumin on the LPS-induced nuclear translocation of NF-κB were examined in RAW264.7 cells (Fig. 2C). Curcumin (50 μM) and monoacetylcurcumin inhibited the 100 ng/ml stimulated NF-κB nuclear translocation, whereas tetrahydrocurcumin did not block the nuclear translocation. In contrast, tetrahydrocurcumin did not suppress IkB phosphorylation (Fig. 2C).

Next, the suppressive effects of curcumin, tetrahydrocurcumin and monoacetylcurcumin on the TNF-α-evoked NF-κB nuclear translocation were investigated in HEK293 cells (Fig. 2C). Inhibition of 20 ng/ml TNF-α-induced NF-κB nuclear translocation by 50 μM curcumin or monoacetylcurcumin was observed, although 50 μM tetrahydrocurcumin did not suppress the nuclear translocation. These results demonstrated that monoacetylcurcumin as well as curcumin suppress the NF-κB nuclear translocation through inhibiting the phosphorylation of IkB.

Anti-oxidative activity has been reported to be linked to anti-inflammatory activity (23). Therefore, we investigated the anti-oxidative activity of curcumin, tetrahydrocurcumin and monoacetylcurcumin against the ROS production induced by TNF-α (Fig. 2D). In HEK293 cells, 50 μM curcumin, tetrahydrocurcumin or monoacetylcurcumin decreased the 50 ng/ml TNF-α-induced ROS production to 60.7, 39.4 and 32.1%, respectively. These results suggest that curcumin, tetrahydrocurcumin and monoacetylcurcumin possess anti-oxidative activity.

The inhibitory activity of curcumin and curcumin derivatives against LPS-induced inflammation in vivo. To assess their anti-inflammatory effects in vivo, we investigated the
The inhibitory activity of curcumin, tetrahydrocurcumin and monoacetylcurcumin against LPS-induced acute inflammation (Fig. 3). Treatment with 250 μg/kg BW LPS significantly increased the serum TNF-α level, and an oral injection of 100 mg/kg BW monoacetylcurcumin decreased the LPS-induced TNF-α production to 36%. Curcumin and tetrahydrocurcumin had no effect. Next, the inhibitory effects of curcumin, tetrahydrocurcumin and monoacetylcurcumin on NF-κB nuclear translocation in the liver were examined. We found that LPS caused the translocation of NF-κB into the nucleus, and monoacetylcurcumin blocked the nuclear translocation, although tetrahydrocurcumin did not have an inhibitory activity of curcumin, tetrahydrocurcumin and monoacetylcurcumin against LPS-induced acute inflammation (Fig. 3). Treatment with 250 μg/kg BW LPS significantly increased the serum TNF-α level, and an oral injection of 100 mg/kg BW monoacetylcurcumin decreased the LPS-induced TNF-α production to 36%. Curcumin and tetrahydrocurcumin had no effect. Next, the inhibitory effects of curcumin, tetrahydrocurcumin and monoacetylcurcumin on NF-κB nuclear translocation in the liver were examined. We found that LPS caused the translocation of NF-κB into the nucleus, and monoacetylcurcumin blocked the nuclear translocation, although tetrahydrocurcumin did not have an
reported that curcumin exerts its anti-inflammatory effect of curcumin is one such biological activity, and it has been various biological activities. The anti-inflammatory activity Numerous studies have demonstrated that curcumin has various biological activities. The anti-inflammatory activity of curcumin is one such biological activity, and it has been reported that curcumin exerts its anti-inflammatory effect through the inhibition of NF-κB nuclear translocation (24). In agreement with a previous study, our results showed that curcumin was able to inhibit the NF-κB nuclear translocation induced by LPS and TNF-α (Fig. 2C) in an in vitro cell culture experiment. In this study, we examined the inhibitory effects of curcumin derivatives against the inflammatory responses in the hope that they possess stronger effects than curcumin. Our previous study found that curcumin is a specific DNA polymerase λ inhibitor of the 10 mammalian DNA polymerase species (16), and the inhibitory effect of monoacetylcumcurcin on DNA polymerase λ activity was the strongest among the 13 chemically synthesized curcumin derivatives including curcumin (17). However, the anti-inflammatory activity of monoacetylcumcurcin is still unknown. Therefore, we investigated the suppressive effects of monoacetylcumcurcin against the LPS- and TNF-α-stimulated NF-κB nuclear translocation and inflammatory responses, although the only difference in chemical structure between monoacetylcumcurcin and curcumin lies in the presence or absence of the acetyl group on the phenyl ring (Fig. 1). Furthermore, our study demonstrated that conjugated bonds in the central seven-carbon chain are important for the suppression of NF-κB nuclear translocation and the subsequent inflammatory responses, since tetrahydrocurcumin did not exert a suppressive effect on inflammation (Fig. 2A-C), and the only difference in chemical structure between curcumin and tetrahydrocurcumin is in several of the conjugated bonds of the central seven-carbon chain (Fig. 1).

In this study, we found that, not only curcumin and tetrahydrocurcumin, but also monoacetylcumcurcin have anti-oxidative activity against TNF-α-induced ROS production and that the order of anti-oxidative ability is monoacetylcumcurcin > tetrahydrocurcumin > curcumin (Fig. 2D). A previous study demonstrated that curcumin derivatives regulate inflammatory responses through a ROS-independent mechanism (15). In fact, our results indicate that the anti-oxidative effects of curcumin and curcumin derivatives are inhibitory effect. Notably, curcumin inhibited NF-κB nuclear translocation although it did not block TNF-α production.

Discussion

Figure 3. The inhibitory activities of curcumin and curcumin derivatives against LPS-induced inflammation in vivo. Male C57BL/6 mice were orally administered curcumin, tetrahydrocurcumin, or monoacetylcumcurcin at 100 mg/kg BW or corn oil as a vehicle control. After 2 h, the mice were intraperitoneally injected with LPS at 250 μg/kg BW or saline as a vehicle control. One hour after the LPS injection, the mice were sacrificed. (A) The TNF-α level in serum was measured using ELISA. Data are shown as the mean ± SE (n=4). Significant difference according to the Student’s t-test (p<0.05). The treatment with corn oil and LPS (positive control) is shown as 100% (TNF-α level, 728 pg/ml) and that with corn oil and saline (negative control) is shown as 0% (TNF-α level, 32 pg/ml). (B) NF-κB p65 in the nuclei of mouse liver cells was detected by Western blotting as described in Materials and methods. The intensity of each band was analyzed, and the values relative to treatment with LPS alone are represented at the lower edge of the image.

monoaetylcumcurcin inhibited NF-κB nuclear translocation in the in vitro-cell culture systems (Fig. 2C) and in vivo (Fig. 3). We also found that monoacetylcumcurcin suppressed the LPS-induced phosphorylation of IκB in RAW264.7 cells. In addition, monoacetylcumcurcin suppressed the LPS-induced increase in the serum TNF-α level, although curcumin had no effect (Fig. 3A). The differences in the actions of curcumin, tetrahydrocurcumin and monoacetylcumcurcin in in vivo experiments may involve their bioavailability. Therefore, the serum levels of curcumin, tetrahydrocurcumin and monoacetylcumcurcin 2 h after their oral administration were measured by a liquid chromatography mass spectrometer. Their serum concentrations were below the detection limit and were <0.3 nM for curcumin and monoacetylcumcurcin, and 3 nM for tetrahydrocurcumin (data not shown). It has been reported that curcumin is difficult to be absorbed into the body (10). A lower level of monoacetylcumcurcin than curcumin and tetrahydrocurcumin might be able to decrease the serum TNF-α level in mice treated with LPS.

Sandur et al investigated the anti-inflammatory effects of curcumin and curcumin analogues, such as emethoxy-curcumin (DMC) and bisdemethoxycurcumin (BDMC), and the order of their suppressive effects on TNF-α-induced NF-κB activation was found to be curcumin > DMC > BDMC (15). Curcumin possesses two phenyl methoxy groups and DMC possesses one. BDMC does not have any phenyl methoxy groups. Therefore, it was suggested that the functional groups on the phenyl ring play a critical role in the inhibition of NF-κB activation. Monoacetylcumcurcin and curcumin include two phenyl methoxy groups, and one of the phenyl methoxy groups of monoacetylcumcurcin possesses an acetyl group (Fig. 1). We showed that monoacetylcumcurcin strongly inhibited the LPS- and TNF-α-stimulated NF-κB activation (Fig. 2C). Notably, monoacetylcumcurcin inhibited the LPS-induced increase in the serum TNF-α level in vivo, although curcumin did not exhibit an effect (Fig. 3A). Therefore, we propose that the acetyl group on the phenyl ring is also involved in stronger suppression of NF-κB nuclear translocation and inflammatory responses, although the only difference in chemical structure between monoacetylcumcurcin and curcumin lies in the presence or absence of the acetyl group on the phenyl ring (Fig. 1).
independent of their inhibitory activity against TNF-α production since tetrahydrocurcumin had no anti-inflammatory effect (Figs. 2A-C and 2D) despite its high anti-oxidative activity (Fig. 2D). These results indicate that the active site(s) of curcumin and curcumin derivatives for inhibition of TNF-α production are different than those for anti-oxidative activity. Previous studies have indicated that the active sites of curcumin and tetrahydrocurcumin related to their anti-oxidative activity are composed of hydroxy and carbonyl groups located in the centers of their chemical structures (15). Furthermore, it has been reported that curcuminoids inhibit T-lymphocyte proliferation independently of their radical scavenging activity; the inhibitory effects were dependent on the number of carbon atoms and doubles of the 1,6-heptadiene-3,5-dione structure as well as on the phenolic ring substitutes of the curcuminoids, and were not correlated to their respective radical scavenging activity (25). Curcumin, tetrahydrocurcumin and monoacetylcurcumin all include hydroxy plus carbonyl groups (Fig. 1). Monoacetylcurcumin exhibited high inhibitory activity against TNF-α production (Figs. 2 and 2D) and anti-oxidative activity (Fig. 2D). Therefore, the acetyl group of monoacetylcurcumin may enhance its anti-oxidative activity using a part of its hydroxy plus carbonyl group.

In conclusion, we found that monoacetylcurcumin, which includes an acetyl group on its phenyl ring, regulates the inflammatory responses by inhibiting IκB phosphorylation and NF-κB nuclear translocation, and the effects of monoacetylcurcumin are more potent than those of curcumin and tetrahydrocurcumin. Our study is the first to demonstrate that monoacetylcurcumin reduces NF-κB activation and TNF-α production. We also suggest the importance of the acetyl group on the phenyl ring in the suppression of inflammatory responses by monoacetylcurcumin. In a previous study, monoacetylcurcumin was reported to exert anti-inflammatory activity in a O-tetradecanoylphorbol-13-acetate-induced ear edema model although its molecular mechanism is yet unknown (26). Since the activated NF-κB was observed in a 12-O-tetradecanoylphorbol-13-acetate-induced ear edema model (27), its anti-inflammatory effects may be at least in part dependent on the inhibition of NF-κB activation. At present, curcumin is regarded as a promising chemopreventive agent against inflammatory responses. Our study indicates that monoacetylcurcumin is useful as an NF-κB inhibitor and may be a potent chemopreventive agent against inflammation.

Acknowledgements

This work was supported, in part, by a grant for the Global COE Program ‘Global Center of Excellence for Education and Research on Signal Transduction Medicine in the Coming Generation’ from the Ministry of Education, Culture, Sports, Science, and Technology of Japan. Tetrahydrocurcumin was kindly provided by Dr Osawa of the Laboratory of Food and Biodynamics, Graduate School of Bioagricultural Science, Nagoya University. Monoacetylcurcumin was kindly provided by the research group of Dr Sugawara of the Department of Applied Biological Science, Tokyo University of Science.

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