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Interaction of Over-the-Counter Drugs with Curcumin: Influence on Stability and Bioactivities in Intestinal Cells

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ABSTRACT: Curcumin, a major constituent in rhizomes of *Curcuma longa* L., has shown various biological activities. It has widely been used as a food additive to provide potential health benefits. In the present study, we investigated changes in chemical stability and cytotoxic properties of curcumin and commonly consumed over-the-counter (OTC) drugs including ibuprofen, acetylsalicylic acid (Asp), and acetaminophen (AAP), through their interactions. Stability of curcumin was significantly improved in phosphate-buffered saline or 0.01 N HCl containing each OTC drug; Asp showed the most prominent effect. Stability of Asp or AAP during 24 h incubation with curcumin was not changed significantly. Cytotoxic effects of curcumin were enhanced in the presence of the OTC drugs on INT 407 normal intestinal and HCT 116 colon cancer cells. Relative cytotoxicity of curcumin (>10 μM) under the drug-treated conditions was significantly higher. Cellular uptake of curcumin in HCT 116 cells increased significantly when incubated with Asp or AAP. Intracellular thiol levels of the cells treated with curcumin were further reduced in the presence of the OTC drugs. The present study provides information that commonly consumed OTC drugs affect chemical stability of curcumin in physiological conditions, and certain bioactivities of curcumin can be altered through their interactions.

KEYWORDS: *curcumin, over-the-counter drug, acetaminophen, aspirin, ibuprofen, cytotoxicity, stability*

INTRODUCTION

Plant-derived natural compounds, also known as phytochemicals, have received intense attention due to their various beneficial effects on health with little toxicity.[1] One of the most studied phytochemicals is curcumin (Figure 1A), a major polyphenolic compound in the dried roots of turmeric (*Curcuma longa* L.), and has been used as a spice and a coloring agent in diverse foods.[2,3] Many physiological effects of curcumin have been reported. Curcumin has antioxidant potential by scavenging various reactive oxygen species (ROS) including superoxide anion, hydroxyl radical, and singlet oxygen.[4,5] Curcumin also inhibits the formation of nitric oxide (NO) either through direct inhibition or inhibiting NO synthase in catalytic and gene expression level.[6,7] Anti-inflammatory, anticarcinogenic, and antidementia activities have also been extensively studied in animal and clinical levels.[8−10] Curcumin is widely applied in many different types of food products including breads, instant rice, and noodles to provide its health beneficial effects. The consumption of curcumin and its related food products has intensely increased in the market.

Over-the-counter (OTC) drugs, including paracetamol (acetaminophen, AAP), acetylsalicylic acid (aspirin, Asp), and ibuprofen (Ibu), are commonly consumed antipyretic and analgesic agents. As nonprescribed drugs, they can be sold directly to a consumer; it may cause an abuse of the drugs with various adverse effects. The drugs are normally metabolized to nontoxic phase II metabolites conjugated with glucuronide, sulfate, and glutathione in the liver, which are excreted through urinary or bile ducts.[11,12] Various dietary phytochemicals go through a similar pharmacokinetic pathway of absorption, distribution, metabolism, and excretion with the drugs consumed; thereby, the constituents in foods and drugs would frequently encounter in the body to result in various interactions.[13,14]

The interactions of drugs with dietary compounds may cause either beneficial or adverse effects. Several types of interactions of drugs with foods or individual dietary compounds have been elucidated. Grapefruits increase the plasma level of cyclosporine, an immunosuppressive drug, through inhibiting efflux by P-glycoprotein.[15] Anthocyanins in cranberry juice also dramatically increase warfarin plasma levels through inhibition of cytochrome P450.[13,14] Accordingly, coadministration of various food constituents and drugs frequently cause changes of their metabolic profiles and bioavailable levels, resulting in decrease or increase of physiological effect of drugs as well as bioactive food compounds in body.[13−15] So far numerous studies have examined the biological activities of curcumin; few research studies, however, have been performed regarding interaction of drugs. Interaction of curcumin with OTC drugs may influence various internal organs from ingestion to excretion. In particular, the intestine is exposed directly to orally administered curcumin or drugs before entering systemic circulation; it could be a valid target site for studying direct interaction of food constituents and drugs even at relatively high concentration. In the present study, we investigated whether chemical features (e.g., stability) are altered through the interaction of curcumin with commonly consumed OTC drugs including Ibu, Asp, and AAP under physiological conditions. Changes in bioactivities of curcumin and the

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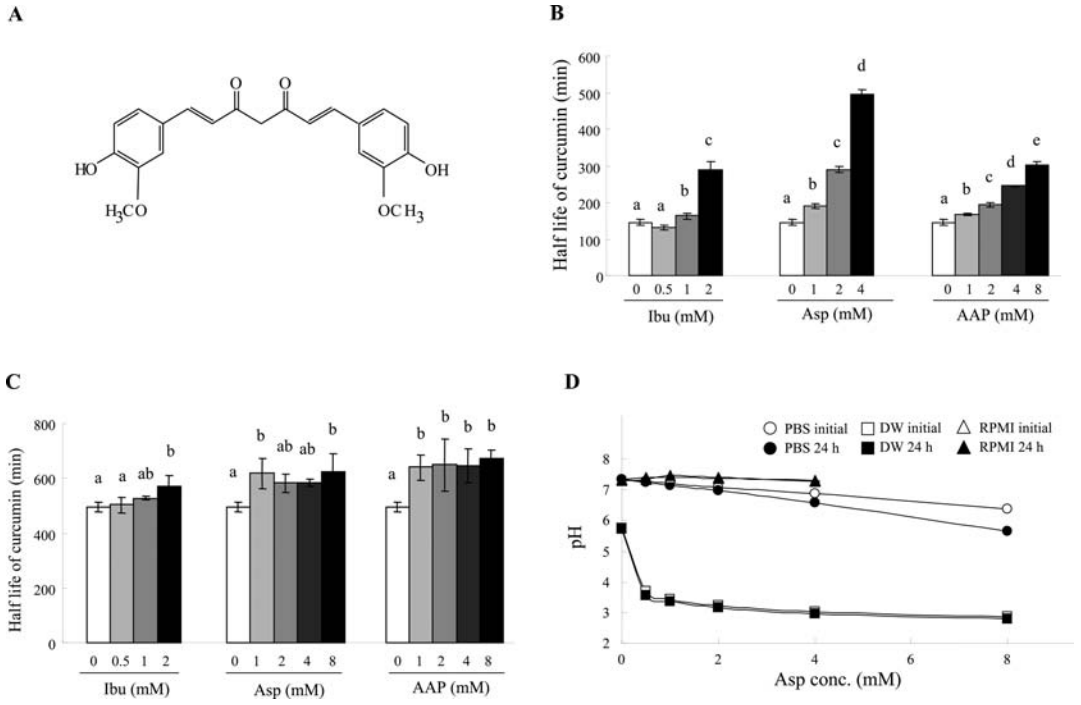

Figure 1. Structure of curcumin (A), changes in curcumin stability by the OTC drugs, and pH changes by Asp. Curcumin (40 μM) was incubated at 37 °C in the absence or presence of different concentrations of Ibu, Asp, and AAP in PBS (B) or in 0.01 N HCl (C). Time-dependent changes in the absorbance values of curcumin for 24 h were analyzed at 405 nm and a half-life of curcumin at each condition was calculated. Changes in pH values of PBS, distilled water, and RPMI culture medium by different concentrations of Asp were also measured (D). Each value represents the mean ± SD (n = 4–8). Different letters indicate a significant difference (p < 0.05) based on one-way ANOVA and the Tukey's HSD test.

OTC drugs through their interaction were also analyzed in intestinal cells.

MATERIALS AND METHODS

Chemicals and Cell Lines. Curcumin [a mixture of curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BMC), approximately 79.4, 16.8, and 3.8% (w/w/w), respectively, average molecular weight 361.05], was purchased from Acros Organics (Morris Plains, NJ). Ibu and Asp were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO). AAP was from Fluka Chemical Co. (Buchs SG, Switzerland), and 3-(4,5-dimethyl-thiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was from Amresco Inc. (Solon, OH). High-performance liquid chromatography (HPLC) grade solvents were obtained from J.T. Baker Co. (Phillipsburg, NJ). All other chemicals were purchased from Sigma-Aldrich Chemical Co. INT 407 human normal intestinal cells and HCT 116 human colon adenocarcinoma cells were obtained from the American Type Culture Collection (Manassas, VA). INT and HCT cells were maintained in Eagle's minimal essential medium (MEM) and in Roswell Park Memorial Institute (RPMI) 1640, respectively, supplemented with 10% fetal bovine serum (FBS), 100 unit/mL penicillin, and 0.1 mg/mL streptomycin. In the MEM medium for INT 407 cells, 1% nonessential amino acids were also added. The cells were kept at 37 °C in 95% humidity and 5% CO_2.

Analysis of Stability of Curcumin and the OTC Drugs. To determine changes in curcumin stability, curcumin (40 μM) dissolved in phosphate-buffered solution (PBS) or 0.01 N HCl were incubated at 37 °C during a 24 h period in the absence or presence of Ibu, Asp, or AAP. At each time point including 0, 0.5, 1, 2, 4, 6, 18, and 24 h, the absorbance of curcumin solution was detected at 405 nm using a microplate reader (Triad LT; Dynex Technologies Inc., Chantilly, VA). Stability of curcumin was also analyzed using HPLC after mixing 50 μL of mobile phase with 150 μL of the curcumin solution incubated for 2 h at the same conditions described above. The mobile phase of HPLC for analyzing curcumin consisted of 60% water containing 1% citric acid and 40% tetrahydrofuran (v/v), and pH was adjusted to 3.0 with concentrated KOH solution.[16] The HPLC system was equipped with a L-6200 intelligent pump (Hitachi, Ltd., Tokyo, Japan), an UV-975 UV/vis detector (Jasco Co., Tokyo, Japan), and a Shiseido C_{18} packed column (150 mm × 4.6 mm, 5 μm particle size). Levels of Asp and AAP were analyzed using an eluent consisting of water/acetonitrile/phosphoric acid (740:180:0.9, v/v/v) and 0.1 M potassium phosphate monobasic/isopropanol/tetrahydrofuran (100:1.5:0.1, v/v/v) with pH 3.7 adjusted by phosphoric acid, respectively.[17,18] Each solvent was run isocratically at a flow rate of 1.0 mL/min and injection volumes were 20 μL. Peaks for curcumin, Asp, and AAP were detected at 420, 237, and 254 nm, respectively.

Analysis of Cell Viability. Effects of curcumin or/and the OTC drugs on viabilities of INT 407 and HCT 116 cells were determined using MTT assay. INT 407 and HCT 116 cells were seeded in 96-well plates at a density of ~1.5 × 10^4 cells per well. The cells were then treated the next day with curcumin, the OTC drugs, or together. After 24 h, compound-containing medium was removed, and 100 μL of fresh serum-free medium containing 0.5 mg/mL MTT was added to each well. The cells were further incubated at 37 °C for 1–2 h. The medium was then removed and replaced by 100 μL of DMSO; the absorbance was measured at 550 nm using a microplate reader (Triad LT).

Analysis of Cellular Levels of Curcumin and Thiol Compounds. To analyze intracellular uptake of curcumin,

HCT 116 cells were seeded in a 6-well plate. When the cells reached ~80% confluency, the cells were treated with 20 μM curcumin in serum-free RPMI medium in the absence or presence of each OTC drug. After 1 h incubation, cells were washed three times with ice-cold PBS containing 0.1% bovine serum albumin, and the cells were lysed with 70% methanol. The cell lysates were centrifuged at 10,000*g* for 10 min at 4 °C. After the supernatant was mixed with an equal volume of HPLC solvent, the mixture (20 μL) was injected onto the HPLC system. The cellular uptake levels were normalized to the protein concentration of each cell lysate determined by a bicinchoninic acid method (Thermo Fischer Scientific Inc., Rockford, IL). For measuring levels of intracellular thiol compound, INT 407 or HCT 116 cells plated in a 96-well plate were treated with curcumin (20 μM) in the presence of different concentrations of each drug. After 2 h of incubation, the medium was replaced with 100 μL of PBS containing 40 μM monobromobimane (mBBr). The cells were further incubated at 37 °C for 30 min and washed by PBS one time. The washing solution was replaced by 100 μL of PBS, and fluorescence value was analyzed at 360 nm excitation and at 465 nm emission (SpectraMax M3; Molecular Devices Inc., Sunnyvale, CA). Each treatment-containing medium (100 μL) collected at 2 h was mixed with 100 μL of 600 μM 2,2-diphenyl-β-picrylhydrazyl (DPPH) solution, and its reducing potential was analyzed measuring absorbance at 517 nm after 30 min of incubation in a dark place (SpectraMax M3).

Data Analysis. Statistical significance was evaluated using Student's *t*-test. One-way analysis of variance (ANOVA) using SAS program (SAS Institute; Cary, NC) and the Tukey's HSD (honestly significant difference) test were also used for comparing multiple results. IC_{50} (concentration that decreases 50% cell viability) values and half-life of curcumin were calculated using the corresponding linear regression equations determined based on the points within a linear range.

RESULT AND DISCUSSION

Modulation of Curcumin Stability by the OTC Drugs. A previous report indicates that absorbance at 405 nm is proportional to curcumin concentrations;[19] the measurement of optical yellowness was commonly applied for assessing curcumin stability.[20,21] Accordingly, we first analyzed changes in stability of curcumin in the presence of OTC drugs measuring the absorbance at 405 nm. The half-life, a period that decomposes 50% of curcumin, was 145 min, when incubated in PBS (pH 7.4) at 37 °C. In the presence of Ibu, Asp, or AAP, fading of curcumin's yellow color was delayed significantly, and their effects were concentration-dependent. Asp showed the most potent stabilizing effect on curcumin; the half-life was prolonged to 494 min in the presence of 4 mM Asp (Figure 1B).

To mimic gastric conditions, curcumin was also incubated in 0.01 N HCl; degradation of curcumin was much slower with a half-life of 495 min. In this condition, the OTC drugs also increased the half-life of curcumin significantly, but the effects were to a lesser extent without showing clear dose dependence (Figure 1C). Curcumin is not stable; various factors are reported to affect curcumin stability including pH, temperature, light, metal ions, oxygen levels, and antioxidants.[20−24] Especially, the pH is one of the most important factors; curcumin is easily decomposed under alkaline conditions. Our results also indicate that half-life of curcumin is more than

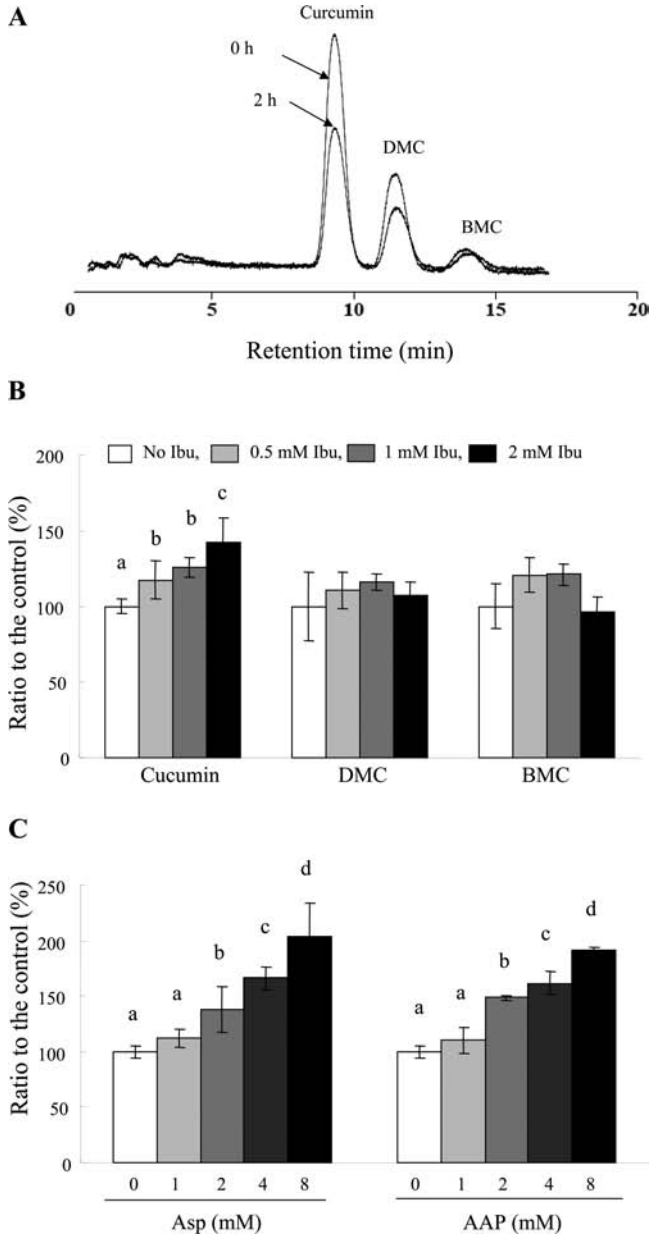

Figure 2. Effects of the OTC drugs on residual curcuminoid levels. (A) Chromatograms of curcuminoids in the present HPLC conditions. A mixture of curcuminoids (40 μM) dissolved in PBS (pH 7.4) was incubated in the absence or presence of different concentrations of Ibu (B), Asp, and AAP (C) for 2 h at 37 °C. Residual levels of curcumin, DMC, and BMC were analyzed using HPLC. Each value represents the mean ± SD (n = 3). Different letters indicate a significant difference ($p < 0.05$) based on one-way ANOVA and the Tukey's HSD test.

threefolds longer in pH 2.0 than in pH 7.4. In both conditions, the OTC drugs significantly improved curcumin stability.

Ibu and Asp are acidic compounds with pK_a ~5.2 and ~3.5, respectively.[25] Their presence could create a more acidic environment, which provides favorable conditions for stabilizing curcumin. We measured pH changes of PBS, distilled water, and RPMI culture medium by Asp. The pH of water dropped rapidly even by 0.5 mM Asp. Initial pH change in PBS was less pronounced, decreasing by 0.49 and 0.97 in the presence of 4 and 8 mM Asp, respectively; it further decreased after 24 h of incubation. Drop of pH by Asp in RPMI medium was much

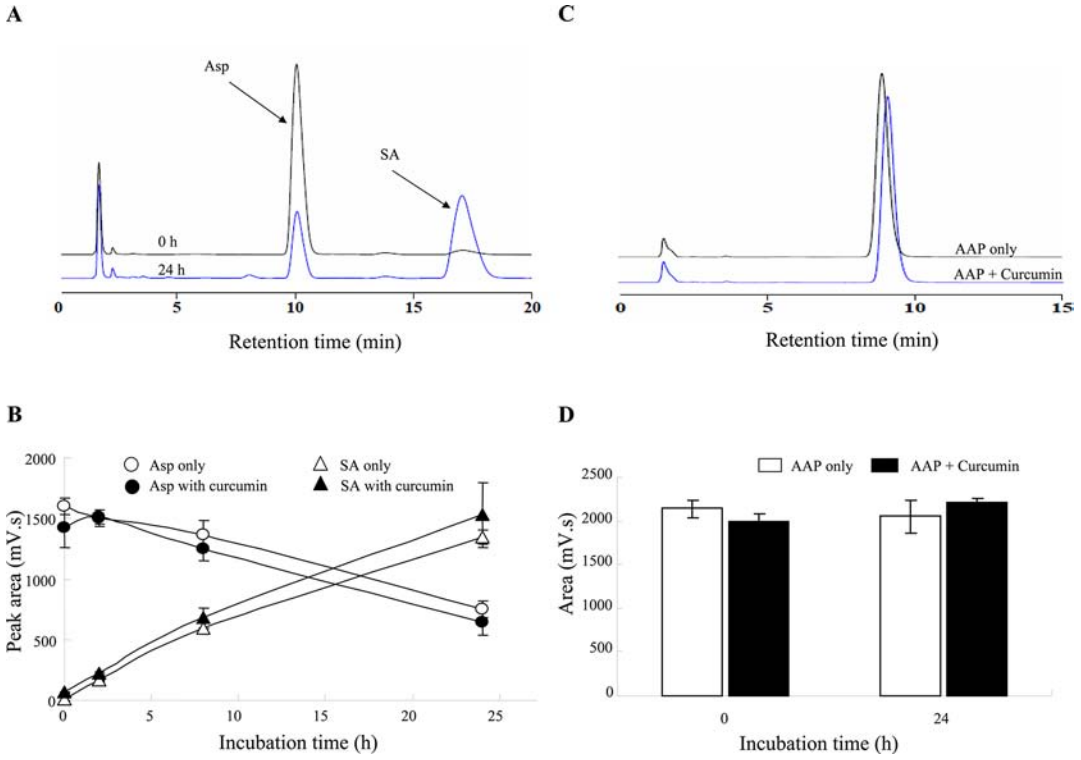

Figure 3. Effect of curcumin on stability of Asp and AAP. (A) Chromatograms of Asp and SA in the present HPLC conditions. Asp (1 mM) was incubated in the absence or presence of curcumin (40 μM) in PBS at 37 °C. At each time point indicated, samples were collected and levels of Asp and SA were analyzed using HPLC (B). A chromatogram of AAP in the current HPLC system was also shown (C). AAP (1 mM) dissolved in PBS was incubated in the absence or presence of curcumin (40 μM) at 37 °C for 24 h. AAP levels from an initial stage and 24 h incubation samples were analyzed using HPLC (D). Each value represents the mean ± SD (n = 3). There is no significant difference between samples according to Student's t-test (in B and D).

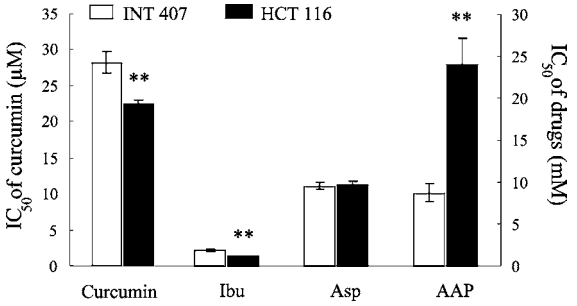

Figure 4. Cytotoxic effects of the OTC drugs and curcumin on the normal intestinal INT 407 or colon cancer HCT 116 cells. INT 407 or HCT 116 cells were incubated with different concentrations of the OTC drugs or curcumin. After 24 h incubation, viable cells were analyzed using the MTT assay and IC_{50} values on each cell line were calculated. Each value represents the mean ± SD (n = 8). **, Significantly different according to Student's t-test ($p < 0.01$).

more marginal (Figure 1D). We also analyzed pH changes by Ibu and AAP; Ibu (1 mM) dropped pH value to a lesser extent as compared to Asp. AAP (8 mM) rather raised the pH of RPMI medium from 7.58 to 7.76. Accordingly, the acidic nature of Asp and Ibu is believed to contribute to their stabilizing effect on curcumin.

It is reported that curcumin decomposition occurred through its oxidation process,[23] and certain types of antioxidants contribute to stabilization of curcumin.[20,24] AAP and Asp are reported to exert an antioxidant role and radical scavenging actions,[26] and the present results also indicate that AAP showed considerable DPPH radical scavenging effects in our experimental system as discussed later. The antioxidant potential of the drugs could play a role in preventing curcumin degradation.

The current curcumin preparation consisted of three curcuminoids containing curcumin, DMC, and BMC. Changes in degradation patterns of individual curcuminoid by the OTC drugs were also investigated using HPLC. In the current HPLC system, three peaks of all curcuminoids were detected (Figure 2A). Among them, curcumin was most unstable and its residual level was only below 50% after 2 h of incubation in PBS, whereas ~80% of DMC still remained, and BMC level was not decreased significantly. The OTC drugs prevented curcumin degradation concentration dependently (Figure 2B,C). The residual DMC and BMC levels were not changed significantly in the presence of the OTC drugs. Improved stability of curcumin in the presence of each drug is in agreement with the results analyzed by absorbance at 405 nm. The results also indicate that stability of curcumin rather than DMC or BMC was most sensitively improved by the OTC drugs. Since the OTC drugs can modulate stability of curcumin under physiological conditions, it is expected that coadministration of the drugs with curcumin also causes changes in absorption and biological activities of curcumin in the body.

Effects of Curcumin on Stability of the OTC Drugs. Effects of curcumin on the stabilities of Asp and AAP were also analyzed. It is reported that Asp is unstable and is rapidly hydrolyzed to salicylic acid (SA).[27] In the current HPLC system, there were two peaks detected including Asp and SA with retention times of ~10 and ~17 min, respectively (Figure 3A). During incubation of Asp (1 mM) with curcumin (40

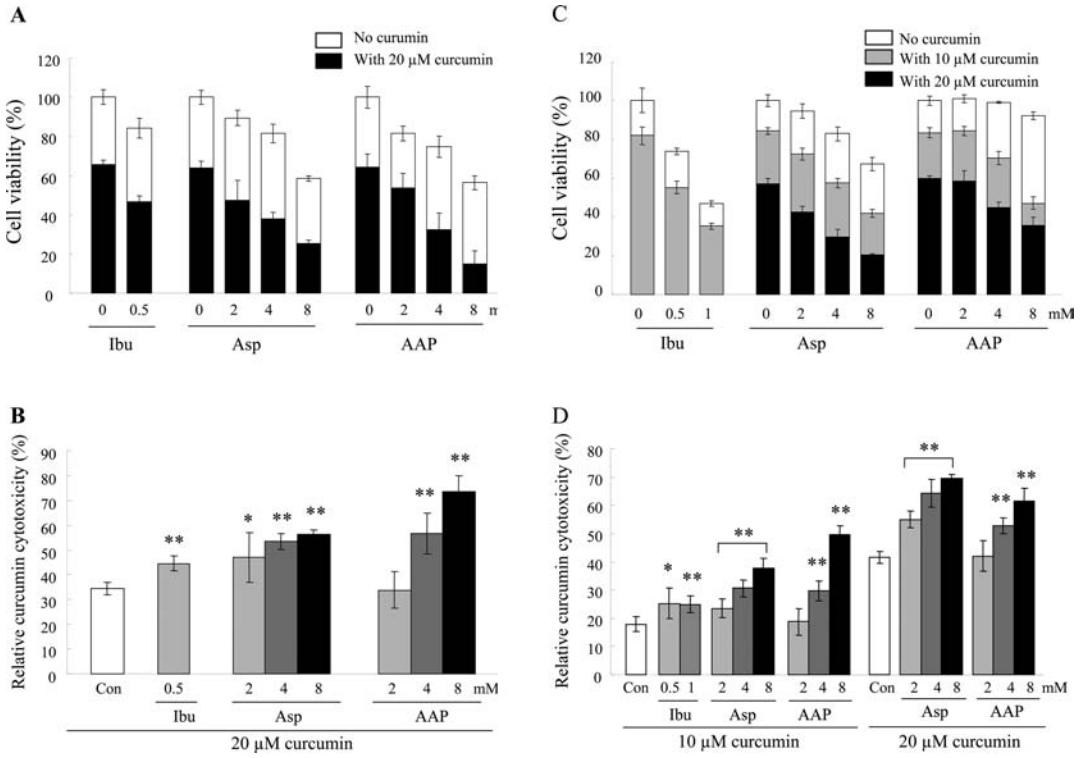

Figure 5. Modulation of cytotoxic properties of curcumin by the OTC drugs. INT 407 (A and B) and HCT 116 (C and D) cells were treated with curcumin in the presence of different concentrations of the OTC drugs. After 24 h of incubation, viable INT 407 (A) or HCT 116 (C) cells were analyzed using MTT assay. The relative toxicities of curcumin against INT 407 (B) or HCT 116 (D) cells under conditions of each drug treatment were also calculated. Each value represents the mean ± SD (n = 8). *, ** Significantly different from curcumin-only control according to Student's t-test (*, $p < 0.05$; **, $p < 0.01$).

μM) in PBS at 37 °C, a peak of SA increased while Asp peak decreased over time; their changes were not altered significantly in the presence of curcumin (Figure 3B).

A peak of AAP was detected with a retention time of ∼9 min in the current HPLC system (Figure 3C). AAP was stable; its level was not significantly changed after 24 h of incubation in PBS at 37 °C and was not affected by curcumin presence either (Figure 3D). The results indicate that curcumin does not affect stabilities of Asp and AAP, although curcumin stability is significantly improved by these drugs.

Cytotoxic Properties of the OTC Drugs and Curcumin. Cytotoxic effects of the OTC drugs and curcumin was investigated using the MTT assay on INT 407 normal intestinal and HCT 116 colon cancer cells. The intestinal epithelium is directly exposed to relatively high concentrations of dietary constituents and drugs ingested before entering the systemic circulation; frequent and direct interactions among these compounds can be expected. After treatment of each drug for 24 h, a dose-dependent decrease of the viabilities was observed in INT 407 and in HCT 116 cells (Figure 4). Among the OTC drugs, Ibu showed the strongest cytotoxic effects on both cell types. Ibu had more potent cytotoxic activity against colon cancer HCT 116 than normal intestinal INT 407 cells; the estimated IC_{50} value, a concentration that inhibits 50% of cell viability, was 1.8 and 1.1 mM on INT 407 and HCT 116 cells, respectively. HCT 116 cells were, however, significantly less sensitive to AAP treatment than INT 407 cells with IC_{50} values of 24.8 and 8.7 mM, respectively. Asp showed similar toxicity to both cell types (Figure 4).

Curcumin also reduced cell viability in a concentration-dependent manner on both cells, showing much more potent cytotoxic activities than the drugs even at micromolar levels. Treatment of curcumin for 24 h resulted in significantly lower viability of HCT 116 cancer cells than that of INT 407 normal cells, with IC_{50} value of 22.5 and 28.2 μM, respectively (Figure 4). This observation is consistent with the previous studies that curcumin caused cancer cell death through induction of apoptosis, but was less cytotoxic to normal cells.[28]

Modulation of Curcumin Cytotoxicity by the OTC Drugs. The present results indicate that curcumin was stabilized in the presence of the OTC drugs, and cytotoxic effects of curcumin on both cells were much more prominent than the drugs. We expected that the interaction of the drugs with curcumin (e.g., modulation of curcumin stability) could affect certain bioactivities of curcumin in cells. Accordingly, effects of curcumin on the viability of INT 407 cells in the presence of the OTC drugs were first analyzed. Curcumin cytotoxicity increased significantly in the presence of the OTC drugs (Figure 5). Sole treatment of 20 μM curcumin caused 65% of INT 407 cell viability; the combined treatment with the drugs further decreased the viable cells concentration dependently (Figure 5A). The relative cytotoxicity of curcumin (the curcumin cytotoxicity calculated based on each control of drug-treated condition) under 0.5 mM Ibu-treated condition was enhanced to 45% from 35% (Figure 5B). Similar effects were also observed when curcumin was treated with Asp or AAP by increasing relative curcumin cytotoxicity to 56% and 73% under 8 mM Asp- and AAP-treated conditions, respectively (Figure 5B).

Modulation of curcumin cytotoxicity by the OTC drugs was also investigated in colon cancer HCT 116 cells. Curcumin at 10 and 20 μM decreased the cell viability by 18% and 42%,

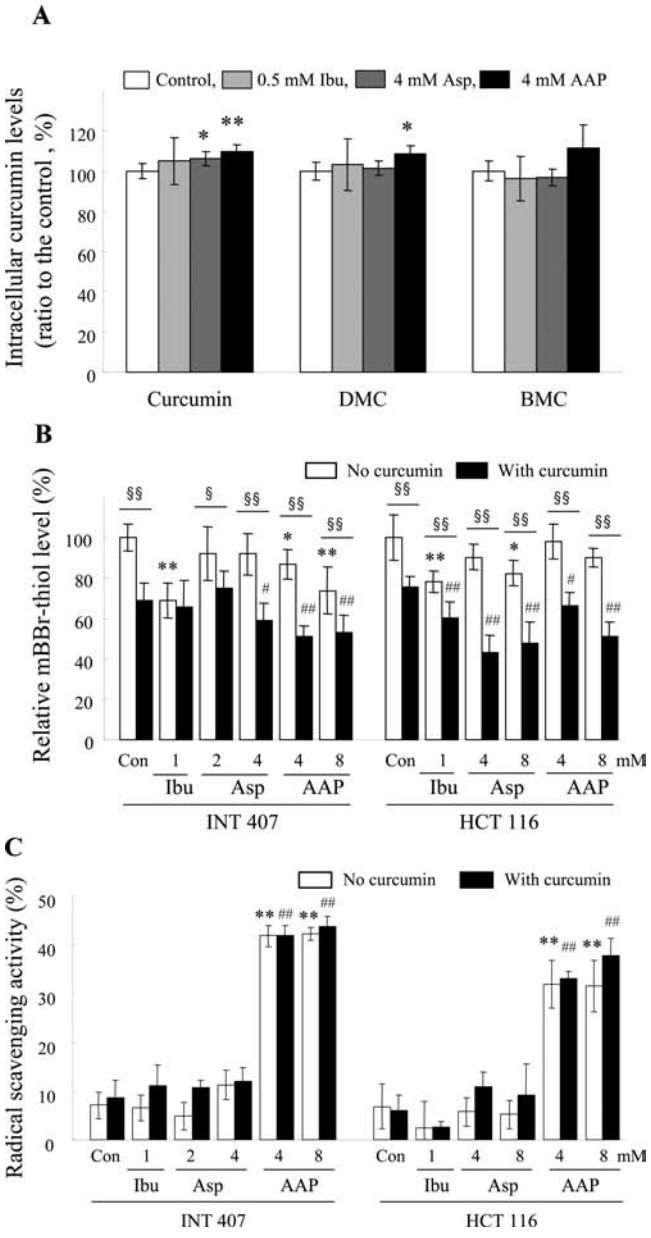

Figure 6. Changes in cellular levels of curcumin and thiol compounds by the OTC drugs and reducing potential of culture media containing curcumin and the OTC drugs. HCT 116 cells were incubated with curcumin (20 μM) in the absence or presence of the OTC drugs. After 1 h of incubation, the cells were lysed and cellular levels of curcumin were analyzed using HPLC (A). INT 407 and HCT 116 cells were also incubated with curcumin (20 μM) with or without the drugs for 2 h. Intracellular levels of thiol compounds in each treated cell were analyzed using mBBr (B). Reducing potential of the culture media from cells treated with curcumin and/or each drug for 2 h were also analyzed based on DPPH radical scavenging activity (C). Each bar represents the mean ± SD (n = 6–8). Significantly different from control (*, $p < 0.05$; **, $p < 0.01$) according to Student's t-test (A). Significant difference from media control (*, $p < 0.05$; **, $p < 0.01$), from curcumin-only control (#, $p < 0.05$; ##, $p < 0.01$), or between only drug and drug with curcumin (§, $p < 0.05$; §§, $p < 0.01$) is also presented (in B and C).

respectively, and the effects were more pronounced in the presence of the drugs (Figure 5C,D). Especially, Asp significantly enhanced curcumin cytotoxicity at all doses treated; the relative cytotoxic effects of curcumin at 10 and 20 μM were enhanced to 24–38% and 55–70%, respectively, under 2, 4, and 8 mM Asp-treated conditions (Figure 5D). Cytotoxic effects of curcumin were also enhanced by cotreated Ibu or AAP except at 2 mM (Figure 5C,D). We have also confirmed the synergistic cytotoxic interaction of curcumin (higher than 10 μM dose) and the OTC drugs on both cell lines based on a classic isobologram analysis; combination points of each drug and curcumin were located below the area of additivity.[29] It should be noted that cytotoxic effects of the combination of the drugs with curcumin especially on INT 407 cells were rather less pronounced in the presence of 10 μM or lower concentrations of curcumin (data not shown). A previous report indicates that sulforaphane, a dietary organosulfur compound, antagonized cytotoxic effects of indomethacin through induction of heme oxygenase-1 (HO-1), that plays a protective role from various cytotoxic events.[30] Curcumin is also known to induce HO-1 in many types of cells,[31] and may play a role in rescuing cells from drug-induced death through induction of HO-1 at a nontoxic dose. A precise mechanism involved in induction of HO-1 by curcumin is now being investigated in our laboratory.

Changes in Cellular Events. It was investigated whether other cellular events are altered by combination treatment of curcumin with the OTC drugs including cellular uptake, intracellular levels of thiol compounds, and reducing status in culture medium. After 1 h of incubation, cellular levels of curcumin significantly increased in the presence of 4 mM Asp and 4 mM AAP. Ibu (0.5 mM), however, was not effective in increasing cellular levels of curcumin in this condition (Figure 6A). Previous studies reported that curcumin reacts with intracellular thiol compounds and decreased the levels including GSH.[32,33] Accordingly, we compared the levels in curcumin-treated cells in the absence or presence of the OTC drugs using mBBr to form a thiol-specific fluorescent adduct. Our results showed that curcumin (20 μM) reduced intracellular thiol levels significantly by 31% and 25% in both INT 407 and HCT 116 cells, respectively. The drugs showed much more marginal effect; only Ibu decreased intracellular thiol levels significantly in both cells. In the presence of the OTC drugs, the levels of thiol compounds in cells treated with curcumin were further reduced significantly (Figure 6B); the decreasing effect was more pronounced in HCT 116 cells. In a simultaneous condition, the reducing status of culture media from curcumin and/or drug-treated cells was also analyzed based on DPPH radical scavenging activity (Figure 6C). Treatment of curcumin did not affect the reducing potential of the culture media significantly; cotreatment of Ibu or Asp with curcumin did not enhance the potential either. The culture medium from AAP-treated cells showed prominent DPPH radical scavenging activity; the reducing potential of AAP could be involved in stabilization of curcumin. It is reported that curcumin stability was improved in the presence of certain antioxidants, and its cytotoxicity enhanced significantly by the antioxidants.[24] Bioactivities of curcumin are closely related to its stability; improved stability of curcumin in the presence of the OTC drugs could cause increased cellular uptake, enhanced cytotoxicity, and other bioactivities of curcumin. Except stability issues, other possible reasons for changes in bioactivities and cellular levels of curcumin (e.g., interaction through efflux transporter and metabolic interactions) can also be considered. In summary, commonly consumed OTC drugs including Ibu, Asp, and AAP affect chemical stability of curcumin in

physiological conditions, and certain bioactivities of curcumin can be altered through their interactions.

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Notes

The authors declare no competing financial interest.

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