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**ARTICLE INFO**

Received on: 27/04/2022
Accepted on: 18/06/2022
Available Online: XX

**Key words:**
Rutin, cyanidin 3-glucoside, metabolizing enzyme, herb–drug interaction, cytochrome P450, transporter.

**ABSTRACT**

Mulberry (*Morus alba* Linn; MA) is a food supplement that may cause herb–drug interactions (HDIs). Potential interactions of MA, its constituents cyanidin 3-glucoside (C3G) and rutin, and four common pharmacologically active agents were examined in HepG2 cells. Cells were incubated with 1–10 μM C3G, 1–10 μM rutin, and 125–500 μg/ml MA alone and in combination with 5 mM acetaminophen (APAP), 5 mM aspirin (ASA), 10 μM simvastatin (SV), or 50 μM caffeine (CF) for 72 hours. The expressions of phase I and II metabolizing enzymes and transporters were determined by RT/qPCR. When tested alone, MA significantly upregulated the expression of *CYP1A2* and UDP-glucuronosyltransferase 1A6 (*UGT1A6*). Cotreatment of HepG2 cells with APAP, ASA, SV, or CF, and MA resulted in upregulation of *CYP1A2* and *N*-acetyltransferase 1 expression and downregulation of ATP-binding cassette B1 and solute carrier organic anion 1B1 expression. Combining MA with APAP, ASA, or SV elevated *CYP2C19* expression, and MA and ASA coinduced the expression of *CYP2D6*. Coadministration of MA with APAP or ASA increased *UGT1A6* expression. C3G and rutin did not affect the expression of any tested genes. Consequently, MA is recommended to be taken at a low dosage due to the feasibility of MA HDIs arising from concomitant use with APAP, ASA, SV, or caffeine.

**INTRODUCTION**

White mulberry (*Morus alba* Linn.; MA) from the Moraceae family has been used in traditional medicine to treat ailments such as blurred vision, fever, high blood pressure, joint stiffness, and urinary tract obstruction (Bae and Suh, 2007). MA contains many bioactive components, including the anthocyanin cyanidin 3-glucoside (C3G) and the flavonoid rutin. C3G has been shown to prohibit invasion and migration of A549 human lung cancer cells by inhibiting the expression of matrix metalloproteinase-2 and the urokinase-plasminogen activator and increasing the expression of the tissue inhibitor of matrix metalloproteinase-2 and the plasminogen activator inhibitor (Chen *et al.*, 2006). In addition, C3G was shown to protect against oxygen–glucose deprivation and glutamate-induced cell death in DIV-7 rat primary cortical neurons (Bhuiyan *et al.*, 2011). Rutin and MA have also been shown to possess potential pharmacological activity; rutin lowered plasma glucose levels in a type II diabetes rat model (Hunyadi *et al.*, 2012), and MA exhibited antihypertensive activity via the inhibition of the angiotensin I-converting enzyme in male Wistar–Kyoto rats (Yang *et al.*, 2012).
The metabolism of xenobiotics primarily occurs in the liver through the combined action of phase I cytochrome P450 (CYP) enzymes such as CYP1A2, CYP2C19, CYP2D6, and CYP3A4; phase II transfers such as sulfotransferase 1A1 (SULT1A1), N-acetyltransferase 1 (NAT1), and UDP-glucuronosyltransferase 1A6 (UGT1A6); and transporters such as ATP-binding cassette B1 (ABCB1) and solute carrier organic anion 1B1 (SLCO1B1) (Estudante et al., 2013; Meyer, 1996). Hence, herbal supplements that interfere with the normal activity of these enzymes and transporters could cause herb-drug interactions (HDIs).

Acetaminophen (APAP) is a common antipyretic and analgesic drug. APAP overdose causes hepatotoxicity due to the production of a toxic metabolite, N-acetyl-p-benzoquinoneimine (NAPQI), during CYP1A2, CYP2E1, and CYP3A4-mediated metabolism (Toes et al., 2005). Aspirin, or acetylsalicylic acid (ASA), is an antiplatelet agent (ASA) that affect CYP metabolism may therefore initiate or increase the risk of an HDI. This study aimed to investigate the impact of MA and other drugs (such as simvastatin (SV), caffeine (CF), and kava kava) on the expression of the pharmacologically important enzymes and transporters, namely, CYP1A2, CYP2C19, CYP2D6, CYP3A4, SULT1A1, NAT1, UGT1A6, ABCB1, and SLCO1B1 in HepG2 cells.

**MATERIALS AND METHODS**

**Reagents**

Cyanidin-3-O-glucoside (C3G) and rutin were supplied by Chengdu Alfa Biotechnology Co., Ltd. (Chengdu, China). Dulbecco’s modified Eagle medium (DMEM) (+) phenol red-free medium, fetal bovine serum, 1× penicillin, streptomycin, and neomycin antibiotics, and 1× GlutaMAX® were supplied by Gibco® (Thermo Fisher Scientific, MA). ReverTra Ace® and random primers were products of Toyobo Co., Ltd. (Osaka, Japan). Primers were synthesized by Bio Basic, Inc. (Markham, Ontario, CA). Taq polymerase and RNase inhibitor were products of Vivantis Technologies Sdn. Bhd. (Selangor, Malaysia). Other chemicals were obtained from commercial suppliers.

**Preparation of mulberry fruit (MA) powder**

Mulberry fruits (Panya, T. 8 KKU No. 25978) were washed in cold water 3× and dried in a hot air oven at 50°C until the moisture content was 10%. The dried fruits were ground and sieved (60 mesh) before storage in a vacuum aluminum package. The contents of C3G and rutin were analyzed by reverse phase high-performance liquid chromatography (RP-HPLC) using a Hypersil octadecyl-silica (ODS) column (4.0 × 250 mm, 5 μm, Agilent Technologies Inc., Santa Clara, CA) with gradient elution of 5%–80% acetonitrile in 0.1% phosphoric acid for 25 minutes at a flow rate of 1 ml/minute coupled with a dual wavelength-UV detector at 517 (for C3G) and 365 nm (for rutin). The MA contained 7.85% C3G and 7.65% rutin dry weight, respectively.

**Cell culture**

HepG2 cells (ATCC® HB-8065, Manassas, VI) were seeded in 24-well plates (2.5 × 104 cells/well) at sterile conditions of 37°C, 5% CO2, and 95% relative humidity for 48 hours. The cells were incubated with 0.2% dimethyl sulfoxide (control), ketoconazole or rifampicin (10 μM), C3G or rutin (1 and 10 μM), MA (125–500 μg/ml), APAP or ASA (5 mM), 10 μM SV, and 50 μM CF for 72 hours. The cells were harvested for total RNA extraction, and mRNA expression was determined using reverse transcription-quantitative polymerase chain reaction (RT/qPCR).

**Determination of mRNA expression by RT/qPCR**

Total RNA was extracted from the cells as previously described (Chatuphonprasert et al., 2015). Concentration and purity of total RNA were assessed using a NanoDrop 2000c U/V-Vis Spectrophotometer (NanoDrop Technologies, Inc., Thermo Fisher Scientific, MA) at 260/280 and 260/230 nm, respectively. Total RNA integrity was examined by 1.25% agarose gel electrophoresis and then converted to cDNA using ReverTra Ace® (Toyobo Co. Ltd., Osaka, Japan) at 25°C for 10 minutes, 42°C for 60 minutes, and 95°C for 5 minutes. cDNA was multiplied to analyze the expression of phase I, namely CYP1A2, CYP2C19, CYP2D6, and CYP3A4, phase II, namely SULT1A1, NAT1, and UGT1A6, transporters, namely, ABCB1 and SLCO1B1, and the reference GAPDH with specific primers for each gene (Table 1) under conditions recommended by the supplier. The mRNA level was normalized to that of GAPDH and expressed as relative fold expression using the delta–delta Ct method as previously described (Chatuphonprasert et al., 2020).

**Statistical analysis**

The results are expressed as mean ± standard deviation. Statistical analysis was performed using one-way analysis of variance with Tukey’s statistical post-hoc test. SPSS version 28.0 (Armonk, NY) was applied for the statistical analysis. Statistical difference was set at p < 0.05.

**RESULTS**

**Modification of phase I metabolizing genes by mulberry fruit (MA) in HepG2 cells**

Expression of CYP1A2 mRNA was upregulated 4.2- and 13.7-fold by 250 and 500 μg/ml MA, respectively, in HepG2 cells after 72 hours treatment (p < 0.05), whereas C3G and rutin did not affect CYP1A2 expression. CYP1A2 expression was also upregulated in a dose-dependent manner after cotreatment of HepG2 cells with APAP and 500 μg/ml MA (5.8-fold), ASA and 250 or 500 μg/ml MA (6.0- and 8.5-fold, respectively), SV and 250 or 500 μg/ml MA (4.5- and 6.7-fold, respectively), and CF and 125, 250, or 500 μg/ml MA (3.8-, 6.1-, and 9.3-fold, respectively) (p < 0.05) (Fig. 1A). The expression levels of CYP2C19, CYP2D6,
and CYP3A4 mRNA were not modified by C3G, rutin, or MA alone (Fig. 1B, C, and D), and APAP, ASA, SV, and CF alone did not alter the expression of CYP2C19. However, cotreatment of HepG2 cells with MA and either APAP (5.4–8.0-fold), ASA (6.0–6.8-fold), or SV (6.0–7.8-fold) did upregulate the expression of CYP2C19 (Fig. 1B). The expression of CYP2D6 mRNA was upregulated 5.7-fold by ASA alone and 2.3–5.1-fold after cotreatment with MA and ASA (p < 0.05) (Fig. 1C). Cotreatment of MA and either APAP, CF, or SV did not significantly change CYP2D6 expression. The expression of CYP3A4 was not modified either by MA alone or by cotreatment with all of the tested agents (Fig. 1D). The known CYP modifiers ketoconazole and rifampicin differently affected CYP expression in HepG2 cells. Ketoconazole elevated CYP1A2 (Fig. 1A) and CYP2D6 (Fig. 1C) expression by 8.7- and 2.5-fold, respectively, while rifampicin induced CYP3A4 expression by 2.6-fold (Fig. 1D). CYP2C19 expression was not changed by either ketoconazole or rifampicin (Fig. 1B).

**Modification of phase II metabolizing genes by mulberry fruit (MA) in HepG2 cells**

After 72 hours, expression of SULT1A1 mRNA was unchanged in HepG2 cells by treatment with either MA alone or in combination with any of the tested agents, while the known CYP modifiers ketoconazole and rifampicin elevated SULT1A1 expression by 3.0- and 1.6-fold, respectively (p < 0.05) (Fig. 2A). The expression of NAT1 mRNA was not altered by treatment with either of the known CYP modifiers, by C3G, rutin, and MA, or by all the tested agents. However, NAT1 expression was upregulated in HepG2 cells by cotreatment with APAP and 500 μg/ml MA (11.5-fold), ASA and 250 or 500 μg/ml MA (5.9- and 19.2-fold, respectively), SV and 125–500 μg/ml MA (10.4-, 13.7-, and 12.8-fold, respectively), and CF and 125–500 μg/ml MA (9.1-, 11.4-, and 5.4-fold, respectively) (p < 0.05) (Fig. 2B). The expression of UGT1A6 mRNA was not altered by rifampicin, C3G, or rutin (Fig. 2C), but MA dose-dependently upregulated UGT1A6 expression resulting in a significant 5.1-fold induction with 500 μg/ml MA (p < 0.05). In addition, UGT1A6 induction was induced by ketoconazole (2.0-fold), by APAP alone (3.9-fold) and with MA (2.6–8.4-fold), and by ASA with MA (1.8–3.2-fold). On the contrary, SV and CF suppressed the expression of UGT1A6 mRNA approximately 0.1-fold (p < 0.05).

**Modification of transporter genes by mulberry fruit (MA) in HepG2 cells**

MA, C3G, and rutin did not modify the expression of ABCB1 and SLCO1B1 mRNA in HepG2 cells after 72 hours treatment (Fig. 3A and B). The expression of ABCB1 was suppressed in HepG2 cells by cotreatment with MA and APAP (0.22–0.33-fold) or ASA (0.26–0.38-fold). ABCB1 expression was suppressed by SV itself (0.26-fold), SV with MA (0.30–0.43-fold), CF itself (0.16-fold), and CF with MA (0.22–0.23-fold) (p < 0.05) (Fig. 3A). The expression of SLCO1B1 was suppressed by cotreatment with MA and APAP (0.21–0.30-fold) and by treatment with ASA alone (0.28-fold), SV alone (0.24-fold), and CF alone (0.18-fold). Cotreatment of HepG2 cells with MA and ASA (0.24–0.36-fold), MA and SV (0.26–0.29-fold), and MA and CF (0.11–0.22-fold) also suppressed SLCO1B1 expression (p < 0.05) (Fig. 3B). Ketoconazole elevated ABCB1 expression 3.7-fold and SLCO1B1 expression 2.0-fold, and rifampicin induced SLCO1B1 expression 1.8-fold (p < 0.05).

<table>
<thead>
<tr>
<th>Genes</th>
<th>Primers (5′→3′)</th>
<th>Annealing temp. (°C)</th>
<th>Product size (bp)</th>
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</thead>
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<tr>
<td>CYP1A2</td>
<td>F ACAAGGGACAACTCGTGA</td>
<td>60</td>
<td>160</td>
</tr>
<tr>
<td></td>
<td>R AGGGCTGTATGAGGAGGAG</td>
<td>60</td>
<td>174</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>F GCAATGTAAGCCACCCTGT</td>
<td>60</td>
<td>174</td>
</tr>
<tr>
<td></td>
<td>R TAAAGTCCCGAGGTTTGGT</td>
<td>60</td>
<td>174</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>F AGCTTTCTGAGCCTCACATC</td>
<td>61.1</td>
<td>135</td>
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<tr>
<td></td>
<td>R GGACCGAGCTTGGCACCACCA</td>
<td>55</td>
<td>87</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>F GGTCCGAGCTCCATTCCTC</td>
<td>60</td>
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</tr>
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<td></td>
<td>R GTGCCGAGCTTCCGTTTTC</td>
<td>55</td>
<td>87</td>
</tr>
<tr>
<td>SULT1A1</td>
<td>F GGAATCCAGGGAAGAGCA</td>
<td>60</td>
<td>151</td>
</tr>
<tr>
<td></td>
<td>R TCAAGTTGCTTCCCTGAG</td>
<td>60</td>
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<tr>
<td>NAT1</td>
<td>F AGCCACGACCTGTGTCCTA</td>
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<tr>
<td></td>
<td>R CCATCTGTGTTGAAAGAGCA</td>
<td>60</td>
<td>110</td>
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<tr>
<td>ABCB1/ P-glycoprotein</td>
<td>F GGATGTCGTAGTGTGAGGG</td>
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<td>SLCO1B1/ OATP1B1</td>
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<td>GAPDH</td>
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Figure 1. Modification of phase I metabolizing genes by mulberry fruit (MA) in HepG2 cells. CT, 0.2% DMSO (control); K, 10 μM ketoconazole; R, 10 μM rifampicin; C3G, cyanidin 3-glucoside; APAP, acetaminophen; SV, simvastatin; CF, caffeine. *p < 0.05 versus CT. n = 4–5.
Figure 2. Modification of phase II metabolizing genes by mulberry fruit (MA) in HepG2 cells. CT, 0.2% DMSO (control); K, 10 μM ketoconazole; R, 10 μM rifampicin; C3G, cyanidin 3-glucoside; APAP, acetaminophen; SV, simvastatin; CF, caffeine. *p < 0.05 versus CT. n = 4–5.
Coadministration of MA with CYP1A2-responsive drugs, such as antipsychotics (e.g., chlorpromazine, clozapine, and olanzapine), naproxen, theophylline, propranolol, and CF (Zanger and Schwab, 2013), or with UGT1A6-responsive drugs, such as valproic acid, APAP, and morphine (Kiang et al., 2005), could result in subtherapeutic levels of these drugs due to the upregulation of CYP1A2 and UGT1A6 expression by MA and subsequent increased rate of metabolism and elimination of these substrates. On the other hand, increased metabolism CYP1A2-responsive prodrugs, such as flutamide, melatonin, and retinoic acid, resulting from coadministration of MA might result in supratherapeutic levels of the pharmacologically active agent (Kang et al., 2008; Nebert and Dalton, 2006). Furthermore, concomitant use of MA with any drug substrates of phase I, CYP1A2, CYP2C19 and CYP2D6, and phase II, NAT1 and UGT1A6, metabolizing genes, and transporters ABCB1 and SLCO1B1 presents a risk for an HDI. The upregulation of CYP1A2 and NAT1 expression by MA combined with APAP, ASA, SV, or CF could result in HDIs with the concomitant use of drugs that are substrates of CYP1A2 or NAT1, such as p-aminosalicylic acid (Kawamura et al., 2005). Importantly, the induction of CYP1A2 might bring about APAP hepatotoxicity. At therapeutic levels, APAP is primarily metabolized via phase II glucuronidation and sulfation with the remainder biotransformed through CYP1A2, CYP2E1, and CYP3A4 metabolism into a toxic byproduct, NAPQI, that is eventually detoxified by the glutathione system (Toes et al., 2005). The upregulation of CYP1A2 mRNA could therefore promote the generation of NAPQI, which would result in excessive generation of reactive oxygen species and initiate lipid peroxidation of cell membranes, resulting in necrosis and/or apoptosis of hepatocytes (Jin and Park, 2012). Notably, the upregulation of UGT1A6 by either MA or APAP would be likely to reverse toxicity from NAPQI accumulation since glucuronidation of APAP is regulated by UGT1A1, UGT1A6, and UGT1A9 (Walter Bock and Köhle, 2005). Not only is caffeine a specific substrate of CYP1A2, but also it can inhibit CYP1A2 activity. One report demonstrated delayed metabolism of anticancer (methotrexate), antidepressant (e.g., amitriptyline, fluvoxamine, and imipramine), antipsychotic (e.g., clozapine, haloperidol, and olanzapine), and cardiovascular (e.g., propranolol, verapamil, and warfarin) drugs after concomitant use with caffeine, due to their common

**DISCUSSION**

![Figure 3. Modification of transporter genes by mulberry fruit (MA) in HepG2 cells. CT, 0.2% DMSO (control); K, 10 μM ketoconazole; R, 10 μM rifampicin; C3G, cyanidin 3-glucoside; APAP, acetaminophen; SV, simvastatin; CF, caffeine. *p < 0.05 versus CT. n = 4–5.](image-url)
metabolizing enzymes (Carrillo and Benitez, 2000). Hence, the coconsumption of caffeine and MA might boost the risk of HDIs due to their synergistic interference with CYP1A2 metabolism. Additionally, CYP1A2 and NAT1 are closely involved in the biotransformation of arylamine procarcinogens into active carcinogens. High levels of CYP1 expression in ER-independent cancers increase the formation of reactive arylamines, which are a particular cause of bladder toxicity and magnify the prospect of bladder cancer (Go et al., 2015). The NAT-catalyzed acetylation of arylamine is associated with carcinogenesis in various organs. For example, the overexpression of NAT1 has been observed in estrogen receptor-positive breast cancer (Sim et al., 2014). Consequently, regardless of any potential HDIs, MA might also promote arylamine-induced carcinogenesis via induction of CYP1A2 and NAT1 expression. On the contrary, since arylamine is also a UGT1A6 substrate (Walter Bock and Köhle, 2005) and UGT1A6 is broadly expressed in many organs of the body, including the esophagus, intestine, kidneys, liver, skin, and urinary bladder, upregulation of UGT1A6 by MA could also feasibly reverse carcinogenesis (Fagerberg et al., 2014).

Cotreatment of MA with APAP, ASA, or SV elevated expression of CYP2C19, which could lead to subtherapeutic levels of co-administered CYP2C19-responsive drugs, such as antidepressants (e.g., amitriptyline and imipramine), voriconazole, progesterone, and omeprazole (Zanger and Schwab, 2013). On the other hand, the antiplatelet prodrug clopidogrel, which needs bioactivation by the CYP2C19 enzyme to become active, might enhance inhibition of platelet reactivity when co-administered with MA and the tested drugs, leading to the risk of bleeding (Sibbing et al., 2010). Previously, CYP2C19 activity was shown to be increased by low-dose ASA (50 mg/day) over 7 days in male nonsmoking healthy volunteers (Chen et al., 2003). In this study, induction of CYP2C19 was not observed by ASA alone, but it was clearly noted after cotreatment with MA. Hence, MA might synergize with ASA to enhance CYP2C19 activity.

The expression of CYP2D6 was significantly induced by cotreatment with MA and ASA. Therefore, the combined use of MA and ASA with CYP2D6 substrates, such as the antidepressant amitriptyline, antihistamines (e.g., diphenhydramine and loratadine), antipsychotics (e.g., aripiprazole, chlorpromazine, and risperidone), cardiovascular drugs (e.g., carvedilol, metoprolol, and propranolol), and opioid derivatives (e.g., codeine, dextromethorphan, and tramadol), might expedite metabolism and elimination of these drugs (Zanger and Schwab, 2013).

The expression of ABCB1 and SLC01B1 was suppressed by cotreatment with MA and the tested drugs. ABCB1, or multidrug resistance 1 (MDR1) encoded P-glycoprotein, is an efflux transporter of harmful xenobiotics and drugs that is located in the intestinal epithelium. Hence, downregulation of ABCB1 might increase the toxicity of some of its substrates, including chemotherapeutics (e.g., cyclosporine, doxorubicin, methotrexate, paclitaxel, and vinblastine), the antidepressant agent clofibrate, the cardiac glycoside digoxin, and hydrocortisone (Estudante et al., 2013). Moreover, some multidrug-resistant cancers utilize ABCB1 as a tool for chemotherapeutic transportation, resulting in resistance to chemotherapeutics such as doxorubicin, paclitaxel, topotecan, and vinblastine (Sharom, 2008). The suppression of ABCB1 expression by cotreatment with MA and APAP, ASA, SV, or CF could be employed as a strategy against this type of MDR.

SLCO1B1 encodes the organic anion transporter polypeptide 1B1 protein, which is a liver-specific influx transporter of endogenous compounds and drugs. Coadministration of MA with the tested drugs could delay the onset of action and/or decrease the efficacy of drugs that use this transporter, such as antibiotics (e.g., cefazolin and rifampicin), the anticancer agent methotrexate, antihypertensive drugs (e.g., enalapril and valsartan), protease inhibitors (e.g., efavirenz and nevirapine), and HMG-CoA reductase inhibitors (e.g., atorvastatin, pravastatin, and rosuvastatin) (Nakanishi and Tamai, 2012).

It is important to note that HepG2 cells have been developed as a surrogate for human hepatocytes in hepatotoxicity screening to overcome the limited availability and phenotypic instability of primary human hepatocyte cultures (Gerets et al., 2012). Nevertheless, various transcriptional regulators in HepG2 cells are known to be expressed at lower levels, including the aryl hydrocarbon receptor, the constitutive androstane receptor, the glucocorticoid receptor, the pregnane X receptor, and the vitamin D receptor (Ani et al., 2006; Tolosa et al., 2016). Therefore, the expression of metabolizing genes in HepG2 cells, including CYP1A1, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4, might deviate from primary hepatocytes, and the present findings should be confirmed in further in vivo and clinical studies.

CONCLUSION

Although MA has been developed as an herbal supplement with promising pharmacological properties, consumption of MA with other pharmaceuticals might give rise to HDIs and undesirable effects through its upregulation of CYP1A2 and UGT1A6. Furthermore, the concomitant use of MA with APAP, ASA, SV, or caffeine extensively modified the expression of several phase I (CYP1A2, CYP2C19, and CYP2D6) and phase II (NAT1 and UGT1A6) metabolizing enzymes and transporters (ABCB1 and SLC01B1). In order to avoid potential HDIs, the use of MA at a low dose and with low frequency is recommended, particularly when used concomitantly with APAP, ASA, SV, or caffeine.

CONFLICT OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

FUNDING

There is no funding to report.

AUTHORS’ CONTRIBUTION

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be authors as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

DATA AVAILABILITY

All data generated and analyzed are included within this research article.
ETHICAL APPROVALS
This study does not involve experiments on animals or human subjects.

PUBLISHER’S NOTE
This journal remains neutral with regard to jurisdictional claims in published institutional affiliation.

REFERENCES


How to cite this article: