Effect of an ethanol extract of *Descurainia sophia* seeds on Phase I and II drug metabolizing enzymes and P-glycoprotein activity *in vitro*

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**Abstract**

**Background:** *Descurainia sophia* seeds have a variety of pharmacological functions and been widely used in traditional folk medicine. However, their effects on human drug metabolizing enzyme (DME) activities have not been elucidated. The present study investigated the inhibitory effects of an ethanol extract of *D. sophia* seeds (EEDS) on human Phase I/II (DMEs) and P-glycoprotein (p-gp) *in vitro*.

**Methods:** The enzyme activities of human Phase I (cytochrome P450s, CYPs), Phase II (uridine diphosphate glucuronosyltransferases, UGTs) DMEs, and the drug transporter P-gp were determined in the presence of various concentrations of EEDS using commercially available luminogenic assay systems. The mode of enzyme inhibition and the inhibitory constant (Kᵢ) value of EEDS were graphically determined with Lineweaver-Burk double reciprocal plots and secondary plots, respectively.

**Results:** The enzyme activity assays showed that EEDS moderately inhibited the CYP1A2, CYP2C9, and CYP2C19 isoforms with half maximal inhibitory concentrations (IC₅₀) of 47.3, 25.8, and 38.7 μg/mL, respectively. Graphical analyses with Lineweaver-Burk double reciprocal plots and secondary plots indicated that EEDS competitively inhibited CYP2C9 with a Kᵢ value of 19.8 μg/mL; however, it inhibited CYP2C9 and CYP2C19 in a mixed mode with Kᵢ values of 5.2, and 11.9 μg/mL, respectively. Other Phase I (CYP2C8, CYP2D6, and CYP3A4) and Phase II (UGT1A1 and UGT2B7) enzymes as well as P-gp were weakly or negligibly affected by EEDS with concentrations up to 500 μg/mL.

**Conclusions:** EEDS is a selective inhibitor of CYP1A2, CYP2C9, and CYP2C19 with moderate enzymatic inhibition. Clinically, full consideration should be given to a potential toxic adverse effect from a herb-drug interaction when drugs that are particularly susceptible to CYP1A2, CYP2C9, or CYP2C19-mediated metabolism are taken together with EEDS. Characterization of metabolic profiles of specific herbal drugs could help consumers and medical specialists to use them safely as a complementary and alternative medicine.

**Keywords:** *Descurainia sophia*, Drug metabolizing enzyme, Herb-drug interaction, Inhibitory effect
Background
In the past few decades, complementary and alternative medicine (CAM) has been combined with conventional medicine to treat diverse diseases. Approximately 38 % of American adults (83 million) are using some form of CAM for their healthcare, and their expenditures on CAM reached $34 billion in 2007 [1]. In Eastern Asia, the prevalence of CAM is much higher, and 76 % of Japanese [2] and 93 % of Chinese cancer patients have used CAM [3]. The proportion of population using CAM in the Republic of Korea was reported as 75 % [4]. In addition, herbal medicines are classified and regulated as formal drugs in these Eastern Asian countries [5].

Herbal medicines comprise an important part of CAM and are used worldwide. Consumers of herbal medicines consider them safe and sometimes forget the fact that herbal extracts contain many phytochemicals and that they can act as substrates, inhibitors, or inducers modulating human metabolic enzymes [6]. The increasing practice of co-administering herbal medicines with conventionally prescribed medications has raised considerably the risk of potential drug-herb interactions, especially in patients who already are on complex treatments involving narrow therapeutic index drugs [1, 7, 8]. Pharmacokinetic herb-drug interactions are one of the major risks caused by phytochemicals modulating the activities of enzymes that metabolize drugs, which subsequently affects their bioavailability [9]. For example, St. John’s wort can decrease the steady state plasma concentrations of cyclosporine, midazolam, tacrolimus, amitriptyline, digoxin, indinavir, warfarin, phenprocoumon, and theophylline [10]. Ginkgo could enhance the hydroxylation of omeprazole by CYP2C19 in a genotype-dependent manner, and garlic could increase the EC₅₀ of warfarin in wild-type vitamin K epoxide reductase complex subunit 1 (VKORC1) in patients [1]. The whole extract of kava, a well-known herbal anxiolytic, can inhibit human CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 in vitro [11] and increase the area under the concentration-time curve (AUC) and the maximum achieved plasma concentration (Cₘₐₓ) of co-administered kawain in vivo [12]. These studies show that determining the effects of individual herbal drugs on human drug metabolizing enzymes (DMEs) is important to predict possible interactions with drugs which can potentially be co-administered in clinics and to reduce the risk of adverse side effects from their concomitant use. Therefore, there is no doubt that chronic users of herbal medications, which are known to inhibit or induce potent human DME activities, should be aware of the potential adverse side effects from herb-drug interactions as well as be carefully advised by medical specialists before their use.

Descurainia sophia (L.) Webb ex Prantl (Flixweed), which belongs to the family Brassicaceae (Cruciferae), originates from Southern Europe and North Africa, and is widely distributed in Northeastern China [13]. The ethnopharmacological uses of D. sophia seeds are to relieve coughing and asthma, treat jaundice, reduce edema, promote urination, etc. [14]. A recent randomized clinical trial showed that the oral administration of D. sophia seeds relieved chronic functional constipation in children which was statistically significant [15]. Some research groups including us have identified various types of secondary metabolites from D. sophia seeds. They are cardiac glycosides, sinapoyl glycosides, flavonoids, lactones, lipids, coumarins, nor-lignans, lignans, and phytosterols [14, 16–21]. The biological activities of some of the isolated phytochemicals are anti-asthmatic, anti-tussive, expectorant [13], and anti-inflammatory as well as cytotoxic activities against human cancer cells [21]. Our previous genome-wide expression analysis showed that the solid fraction of the ethanol extract of D. sophia seeds regulated diverse genes which are closely associated with several biological functions like cell survival and death [22].

As evidence for the ethnopharmacological use of D. sophia seeds increases, the clinical applications and medicinal requirements of D. sophia seeds may increase gradually. However, no scientific study is currently available showing the effects of D. sophia seeds on the activities of human DMEs. The goal of the present study was to elucidate the inhibitory effect of D. sophia seeds on major human DMEs including Phase I (cytochrome P450s, CYPs) and Phase II (uridine diphosphate glucuronosyltransferases, UGTs) enzymes and a drug transporter (P-glycoprotein, P-gp).

Methods
Plant materials and extract preparation
The dried seeds of D. sophia were purchased from Kwang-myungdang Medicinal Herbs Co. (Ulsan, Republic of Korea). D. sophia seeds were collected in the Shandong Province, China in June 2010 which was written on the batch label. They were identified by Dr. Go Ya Choi at the K-herb Research Center, Korea Institute of Oriental Medicine, Daejeon, Republic of Korea. A voucher specimen (KIOM-CRC-5) was deposited at the KM-Convergence Research Division, Korea Institute of Oriental Medicine. Whole extract of the dried seeds of D. sophia was prepared by repeated maceration in 80 % (v/v) ethanol. The solid phase of the ethanol extract (EEDS) was further concentrated and dried. Finally, the EEDS was stored at 4 °C. The EEDS was dissolved in 100 % dimethylsulfoxide (DMSO, Sigma, St Louis, MO, USA) to make a stock solution and then stored at -80 °C until used. A detailed procedure on preparing EEDS was described previously [22].

Luminogenic DME inhibition assays in vitro
In vitro enzymatic inhibition assays of human Phase I (CYPs) and Phase II (UGTs) DME, and P-gp were done

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with commercially available luminogenic assay systems. The assay systems were purchased from Promega (Madison, WI, USA), and the microsomes containing the recombinant human CYPs were purchased from Life Technologies (Carlsbad, CA, USA). The microsomes containing human UGT and P-gp were supplied in the luminogenic assay systems (Promega). The details on the assay systems and the microsomes are presented in Table 1. The activity for each enzyme was determined in the presence and absence of serially diluted EEDS. A known specific enzyme inhibitor was included as a positive control to verify the validity of each assay system. They are also summarized in Table 1. The maximum tolerable concentration of the vehicle (DMSO) was adjusted to 0.25 % (v/v) for all enzyme activity assays except for the DMSO-sensitive CYP2C8 (0.05 %). The enzyme reaction was done according to the manufacturer’s instructions. The luminescent intensity, which is correlated with the enzyme activity, was quantified with a TriStar LB 941 multimode microplate reader (Berthold Technologies, Bad Wildbad, Germany). The modulated enzyme activity by EEDS was evaluated by comparing the changes in activity from the treatment with the solvent alone to those from the treatment with the EEDS. The apparent half-maximal inhibitory concentration (IC\textsubscript{50}) was determined with the SigmaPlot program (version 11.0, Systat Software, Inc, San Jose, CA, USA) with a 4-parameter logistic equation.

### Statistics

The data are presented as the means \pm standard deviation (S.D.) for at least duplicate experiments. The means and S.D. were determined with the SigmaPlot program.

### Results

**Inhibitory effects of EEDS on human DME activities**

The inhibitory effect of EEDS on human DME activities were evaluated with the \textit{in vitro} luminescent assay described earlier. The calculated IC\textsubscript{50} of the EEDS and specific inhibitors against each DME are presented in Table 3. The inhibitory potencies of the test drugs were classified as potent (IC\textsubscript{50} \leq 20 \mu g/mL for crude extract or IC\textsubscript{50} \leq 10 \mu M for a single compound), moderate (20 < IC\textsubscript{50} < 100 \mu g/mL or 10 < IC\textsubscript{50} < 50 \mu M), or weak (IC\textsubscript{50} \geq 100 \mu g/mL or IC\textsubscript{50} \geq 50 \mu M) [24]. According to this categorization, the EEDS exhibited a moderate inhibitory effect on the CYP1A2, CYP2C9, and CYP2C19 isoforms with an IC\textsubscript{50} of 47.3, 25.8, and 38.7 \mu g/mL, respectively. However, CYP2C8 (IC\textsubscript{50} > 100 \mu g/mL), CYP2D6 (IC\textsubscript{50} = 137.5 \mu g/mL), and 3A4 (IC\textsubscript{50} = 134.2 \mu g/mL) were weakly inhibited by EEDS. The effect of EEDS on UGT1A1 was very weak (IC\textsubscript{50} = 335.1 \mu g/mL) and on UGT2B7 and P-gp negligible (IC\textsubscript{50} > 500 \mu g/mL).

**Determining the mode of enzyme inhibition and the K\textsubscript{i} value**

Next, we determined the K\textsubscript{i} values and the mode of enzyme inhibition for the CYP1A2, CYP2C9, and CYP2C19 isoforms with an IC\textsubscript{50} less than 100 \mu g/mL for Table 2. The mode of enzyme inhibition was graphically determined from the Lineweaver-Burk double reciprocal plots. The K\textsubscript{i} value was calculated with the secondary plot representing the slope rate of the Lineweaver-Burk plot versus the EEDS concentrations (0, 12.5, 25, 50, and 100 \mu g/mL) [23].
the EEDS. From the results, the EEDS competitively inhibited CYP2C9 but showed mixed inhibition for CYP1A2 and CYP2C19 seen in the Lineweaver-Burk double reciprocal plots (Fig. 1). The calculated Kᵢ values for CYP1A2, CYP2C9, and CYP2C19 were 19.8, 5.2, and 11.9 μg/mL, respectively (Fig. 1). Therefore, the most potent inhibition by the EEDS was for CYP2C9 followed by CYP2C19 and CYP1A2.

**Discussion**

The effect of a potential drug candidate on human DMEs, such as the induction or inhibition of CYPs, can be a safety issue because it can change the metabolism of other co-administered xenobiotics or drugs unintentionally, and subsequently enhance or reduce their pharmacological or toxic profiles [25, 26]. In vitro enzymatic studies of human cytochrome P450 modulated by a specific compound are considered cost-effective in predicting the potential drug-drug interaction in clinical trials [27]. In this study, we evaluated the modulation of human DME and P-gp activities in vitro with ethanol extracts of *D. sophia* seeds. *D. sophia* seeds have been prescribed as a folk medicine worldwide to treat or relieve diverse diseases and symptoms, especially in eastern Asian countries. *D. sophia* seeds have been traditionally used as a component of herbal prescriptions. They have been taken as a water extract after decoction or a round pill just after grinding them. Therefore, taking into consideration the conventional intake methods, we used repeated maceration in 80 % ethanol to extract the active ingredients as much as possible.

In our previous study, we reported on the anticancer effects of EEDS against various human cancer cell lines and identified various bioactive constituents from EEDS [21, 22]. Fourteen compounds were isolated from the ethanol extract of *D. sophia* seeds by chromatographic separation methods. Among them, helveticoside showed the most potent cytotoxicity with an IC₅₀ ranging from 0.034 to 0.596 μM depending on the human cancer cell line. Quercetin and syringaresinol exerted dose-dependent inhibitory effects on NO production in LPS-stimulated RAW264.7 cells with median effective doses (ED₅₀) of 5.5 μM and 10.0 μM, respectively. Several research groups have reported on the biological activities of *D. sophia* seeds. Khodarahmi et al. evaluated the cytotoxic effects of volatile oil from *D. sophia* seeds on the MCF-7 and HeLa cell lines with an IC₅₀ of 70 μg/mL and 180 μg/mL, respectively [28]. Gong et al. reported on the in vivo anti-asthmatic, anti-tussive, and expectorant activities of *D. sophia* seed oil supporting the ethnopharmacological use of *D. sophia* seeds to relieve respiratory diseases [13]. To the best of our knowledge, the present study is the first to report the effect of the whole extract of *D. sophia* seeds on human DMEs and P-gp. Biochemical luminogenic inhibition assays showed that human CYP1A2, CYP2C9, and CYP2C19 were moderately inhibited by EEDS based on their pharmacokinetic parameters (IC₅₀ and Kᵢ). Other tested CYP isotypes including CYP2C8, CYP2D6, and CYP3A4, were weakly inhibited by EEDS. These results show that the bioavailability of drugs, which are metabolic substrates of CYP1A2, CYP2C9, or CYP2C19, can be affected when these drugs are concomitantly administered with EEDS, causing potential adverse effects by elevating

| Table 2 | Summary of reaction conditions to determine modes of CYP enzyme inhibition and Kᵢ values |
| Parameters | CYP1A2 | CYP2C9 | CYP2C19 |
| Substrate (μM) | Luciferin-ME | Luciferin-H | Luciferin-H EGE |
| (12.5 ~ 100) | (25 ~ 200) | (2.5 ~ 20) |
| Enzyme (pmol) | 0.5 | 0.5 | 0.25 |
| EED5 (μg/mL) | 0-100 | 0-100 | 0-100 |
| Incubation time (min) | 10 | 30 | 20 |
| Temperature (°C) | 37 | 37 | 37 |

| Luciferin-ME luciferin 6-methyl ether, Luciferin-H 6-deoxyluciferin, Luciferin-H EGE ethylene glycol ester of 6-deoxyluciferin |

| Table 3 | IC₅₀ of EEDS on human DMEs |
| Types | DMEs | Inhibitors | IC₅₀ EEDS (μg/mL) | Inhibitors (μM) |
| Ph I | CYP1A2 | α-naphthoflavone | 47.3 ± 7.0 | 0.22 ± 0.03 |
| | CYP2C8 | Montelukast | >100 | 0.31 ± 0.02 |
| | CYP2C9 | Sulfaphenazole | 25.8 ± 1.9 | 0.13 ± 0.01 |
| | CYP2C19 | Ticlopidine | 38.7 ± 2.5 | 0.39 ± 0.03 |
| | CYP2D6 | Quinidine | 137.5 ± 0.3 | 0.08 ± 0.00 |
| | CYP3A4 | Ketoconazole | 134.2 ± 3.5 | 0.25 ± 0.03 |
| Ph II | UGT1A1 | Diclofenac | 335.1 ± 57.3 | 180.3 ± 29.6 |
| | UGT2B7 | Diclofenac | >500 | 179.4 ± 30.9 |
| Drug transport | P-gp | Na₃VO₄ | >500 | 3.40 ± 0.32 |

*Values are expressed as the means ± S.D. of at least duplicated experiments*
Fig. 1 Left panel, primary Lineweaver-Burk plots for CYP1A2, CYP2C9, and CYP2C19. The modes of enzyme inhibition were determined by incubating an enzyme with a combination of different concentrations of EEDS and increasing the concentrations of specific substrates. Right panel, secondary plots for CYP1A2, CYP2C9, and CYP2C19. $K_i$ value was calculated by the secondary plot representing the slope rate of the Lineweaver-Burk plot versus increasing the concentrations of EEDS. Minus $K_i$ values ($-K_i$) from the plot intersect on the x-axis.
EEDS. Therefore, EEDS may only slightly affect the activity of UGTs in the present study. The effects on these two UST isotypes were negligible.

The P-gp protein is an ATP-dependent drug efflux transporter and also known as multidrug resistance 1 (MDR1) or ATB-binding cassette subfamily B member 1 (ABCB1). When the distribution of P-gp was determined using a monoclonal antibody raised against P-gp, the distribution of human P-gp in normal tissues was concentrated in cells found in the intestinal epithelium, liver, proximal tubule of the kidney, and capillary endothelium, where it pumps back toxic materials into the intestinal lumen, bile and urinary ducts, and capillaries, respectively [36–38]. Many studies reported that P-gp can interact with herbal decoctions or extracts and with phytochemicals isolated from medicinal herbs [36, 37, 39–41]. Administration of herbal medicines that affect P-gp activity can induce enhanced drug toxicity or improve intracellular drug transport by inhibiting the P-gp mediated drug efflux. In the present study, however, EEDS did not modulate the verapamil-stimulated ATPase activity of P-gp up to the maximum concentration of EEDS (500 μg/mL) tested in our biochemical assay system.

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Some constituents of *D. sophia* seeds were evaluated for their effects on human DMEs. Quercetin, a flavonoid, is a potent competitive inhibitor of CYP1A2, CYP2C, CYP2C19 and CYP3A4 ($K_i = 0.93, 1.67, 1.74$ and $4.12 \mu M$, respectively) [42], and inhibits human UGT1A1B, a key steroid-metabolizing enzyme [43]. Additionally, Choi et al. reported that enhanced doxorubicin absorption in the gastrointestinal tract is attributed to quercetin-induced inhibition of P-gp and that the first-pass metabolism of doxorubicin is attributed to quercetin-induced inhibition of CYP3A in the small intestine [44]. Syringaresinol, another constituent of *D. sophia*, exhibited inhibitory effects on P-gp in adriamycin-resistant human breast cancer cells, MCF-7/ADR [45].

**Conclusions**

*In vitro* enzyme activity assays showed that EEDS modulates the activities of human Phase I/II DMEs and P-gp to varying degrees of potency indicating the potential risk of herb-drug interactions. CYP2C9 was competitively inhibited; however, CYP1A2 and CYP2C19 were inhibited in a mixed manner by EEDS with $K_i$ values of $19.8, 5.2,$ and $11.9 \mu M$, respectively, CYP2C8, CYP2D6, CYP3A4, UGT1A1, UGT2B7, and P-gp were not weakly or negligibly affected by EEDS. In the present study, however, the bioactive constituent(s) responsible for affecting the enzyme activities were not identified. Further studies will have to be done to identify the preferred phytochemical constituents and their enzyme modulating properties. In addition, we should keep in mind that various *in vivo* factors could influence *in vitro* to *in vivo* extrapolation.

**Abbreviations**

ABC1: ATB-binding cassette subfamily B member 1; AUC: area under the concentration-time curve; CAM: complementary and alternative medicine; $C_{\text{max}}$: maximum achieved plasma concentration; CYP: cytochrome P450; DME: drug metabolizing enzyme; DMDS: dimethylsulfoxide; ED$_{50}$: median effective doses; EEDS: ethanol extract of *D. sophia* seeds; $IC_{50}$: half maximal inhibitory concentrations; $K_i$: inhibitory constant; MDR1: multidrug resistance 1; P-gp: P-glycoprotein; UGT: uridine diphosphate glucuronosyltransferases; VKORC1: vitamin K epoxide reductase complex subunit 1.

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

JMY and NSK developed the study concept and experimental design, performed data acquisition and analysis, and drafted the manuscript. YJL and YAK performed data acquisition and analysis, and assisted with the revision of the manuscript. OSB supervised the entire study and assisted with the revision of the manuscript. All authors read and approved the final manuscript for submission.

**Acknowledgments**

This research was supported by a grant from the Korea Institute of Oriental Medicine (K15261).

Received: 17 August 2015 Accepted: 9 December 2015

Published online: 18 December 2015

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