# The Role of *Andrographis paniculata* (Burm.f.) Wall. ex Nees in Drug Interactions

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## ABSTRACT

  *Andrographis paniculata* (Burm.f.) Wall. ex Nees, commonly known as Fa-tha-lai-jone is an herbal medicine in The National List of Essential Drugs A.D.2013. The aerial part of the plant is used for treatment of non-infectious diarrhea and common cold. *A. paniculata* extract and its major active component, andrograpolide, have various pharmacological activities. Therefore co-administration of *A. paniculata* with conventional drugs may cause unpleasant interactions. This article reviews the role of *A. paniculata* and its active component that influences drug interactions including the effect on phase I and phase II metabolizing enzymes as well as drug transporter protein. Furthermore the data of pharmacokinetic and pharmacodynamic interactions on some clinical drugs are also included.

**Keywords:** *Andrographis paniculata*, andrographolide, cytochrome P450, herb-drug interaction

## INTRODUCTION

Thailand's Ministry of Public Health has launched a policy to promote the use of medicinal plants in primary health care since 1977 (the 4th National Health Development Plan) until present (the 11th National Health Development Plan).[1] A number of herbal medicines have been selected to include into the National List of Essential Drugs and the first list was approved in 1999. Nowadays the latest list, approved in 2013, covers 50 traditional medicines and 24 single herbal medicines. Thai Food and Drug Administration classified herbal medicinal products into four categories including: (i) traditional drugs, (ii) modified traditional drugs, (iii) modern herbal medicines, and (iv) new drugs. Most Thai traditional medicines and herbal medicines fall into the first three categories of herbal medicinal products.[2-3] *Andrographis paniculata* (Burm.f.) Wall. ex Nees, commonly known as Fa-tha-lai-jone, has been one of the medicinal plants placed in the list of herbal medicinal products for treatment of non-infectious diarrhea and common cold in The National List of Essential Drugs A.D.2013.[3] The monograph of *A. paniculata* was published in the Thai herbal pharmacopoeia (THP), volume 1 which was issued in 1995 by the Department of Medical Sciences, Ministry of Public Health and in the WHO Monograph on Selected Medicinal Plants, volume 2.

  *A. paniculata*, belonging to the family Acanthaceae, is widely distributed in tropical and subtropical Asia, south-east Asia and India. It is an annual branched herb with extremely bitter taste in every part of the plant. The stems are dark green, 0.5-1 m in height and 2-6 mm in diameter

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with presence of longitudinal furrows and wings on the angles of young plants and slightly enlarged at the nodes. The leaves are 3-7 cm long, 1-2.5 cm wide, green, simple, opposite decussate, lanceolate and glabrous with short petiole, and often copper shade coloration above at edges during flowering. Flowers are small, in lax spreading axillary and terminal racemes or panicles, white in color with reddish-purple spots on the petals. Fruit is simple, dry dehiscent, capsule laterally flat with 2 distinct lobes, 1.2-1.7 cm long, 2-3.5 mm wide, dull brown color and dehiscent loculicidal at maturity. Seeds are small, numerous, and yellowish brown in color.[4-6] The aerial parts of *A. paniculata* are used as traditional medicine in the form of powdered crude drug. The optimum harvesting period of the drug is about 3-5 months old or at 50% blossom which gives the highest quantity of active lactone compounds.[4] The indications are relief of non-infectious diarrhea with the daily dose ranging from 2-8 g (in 4 equally divided doses) and relief of common cold with the daily dose ranging from 6-12 g (in 4 equally divided doses).[3]

## Chemical constituents

The major constituents of the aerial parts of *A. paniculata* are diterpene lactones in free and glycosidic forms (Fig 1), including andrographolide, 14-deoxyandrographolide, 11,12-didehydro-14-deoxyandrographolide, neoandrographolide, andrographiside, 11,12-didehydro-14-deoxyandrographiside, and andropanoside.[5] Among these compounds, andrographolide ($C_{20}H_{30}O_5$; 3-[2-{decahydro-6-hydroxy-5-(hydroxymethyl)-5,8$\alpha$-dimethyl-2-methylene-1-napthalenyl} ethylidene]dihydro-4-hydroxy-2(3H)-furanone) is the primary bioactive compound presenting in all parts of the plant, maximally in the leaves. It is colorless, crystalline, and bitter taste with melting point at 230-239°C.[6-8] According to Thai Herbal Pharmacopoeia, the powdered crude drug from aerial parts of *A. paniculata* contains not less than 6% of total lactones, calculated as andrographolide and the capsule dosage form contains an amount of the powdered crude drug equivalent to not less than 80.0% and not more than 120.0% of the labeled content of total lactones, calculated as andrographolide.[9-10]

## Pharmacokinetic studies

A pharmacokinetic study of andrographolide in 16 healthy volunteers revealed that andrographolide is highly absorbed from gastrointestinal tract into blood after taking a single oral therapeutic dose of Kan Jang tablets (equivalent to 20 mg of andrographolide). The maximum plasma level of andrographolide is approximately 393 ng/ml (1.12 μM) within 1.5-2 hours after oral administration. Half-life and mean residence times are 6.6 and 10.0 hours, respectively. More than 90% of andrographolide is eliminated by metabolic transformation.[11] After oral administration of andrographolide, the metabolites isolated from rat urine, feces, and the contents of the small intestine are mainly identified as sulfonic acid adducts and sulfate compounds.[12] One of those metabolites, 14-deoxy-12(R)-sulfoandrographolide, is identical to an anti-inflammatory drug (Lian-bi-zhi) which is clinically used as an injection in China.[6,13] The metabolites of andrographolide isolated from human urine are sulfates and cysteine S-conjugate (Fig 2).[14]
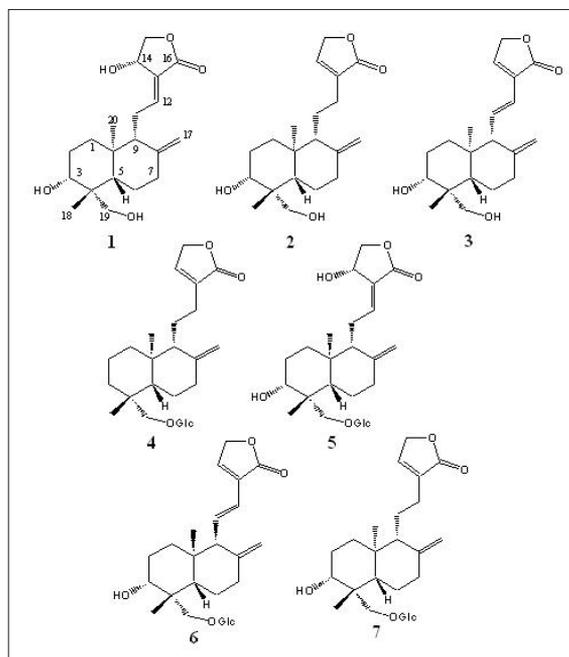


**Fig 1.** Major constituents of the aerial parts of *A. paniculata*: (1) andrographolide, (2) 14-deoxyandrographolide, (3) 11, 12-didehydro-14-deoxyandrographolide, (4) neoandrographolide, (5) andrographiside, (6) 11,12-didehydro-14-deoxyandrographiside, and (7) andropanoside. (All chemical structures were drew using CS ChemDraw Ultra 6.0 software, according to reference 5)
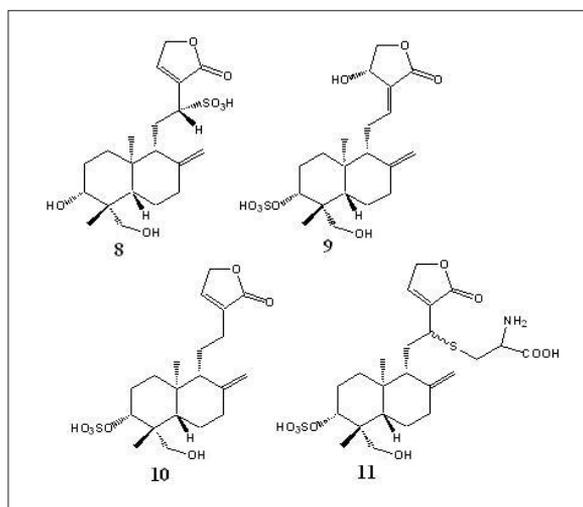
**Fig 2.** Metabolites of andrographolide isolated from human urine: (8) 14-deoxy-12(*R*)-sulfoandrographolide, (9) andrographolide-3-*O*-sulfate, (10) 14-deoxyandrographolide-3-*O*-sulfate, (11) 14-deoxy-12-(cysteine-S-yl)-andrographolide-3-*O*-sulfate. (All chemical structures were drew using CS ChemDraw Ultra 6.0 software, according to reference 12-14)

## The role of *Andrographis paniculata* (Burm.f.) Wall. ex Nees in drug interactions

Consumers generally belief that herbal medicinal products are safe as they are natural therefore the products are often taken without consulting a physician. In point of fact, herbal medicinal products consist of a combination of compounds which possess potentially pharmacological activities. As a result interactions between herbal medicinal products and conventional drugs, which are called herb-drug interactions, can occur. The outcome from herb-drug interactions can be harmful if it causes an increase in the toxicity or reduction in efficacy of drug. It is difficult to identify herb-drug interactions due to non-reporting usage from patients, variability of chemical constituents of herbal medicines, a lack of pharmacological data of herbal medicines, and poor characterization of mechanisms of action of herbal medicines.[15-16] Comparable to drug-drug interactions the mechanisms of herb-drug interactions involve the pharmacokinetic and pharmacodynamic reactions. Pharmacokinetic interactions are those in which herbal medicines affect the absorption, distribution, metabolism, and excretion of the drugs while pharmacodynamic interactions are those in which the effects of a drug are changed by the presence of herbal medicine at its site of action.[17]

## The effects of *A. paniculata* and its major active components on phase I metabolizing enzyme, CYPs

Many evidences have indicated that *A. paniculata* and its major active component, andrographolide, demonstrate the influence towards the pharmacokinetic behavior of drugs. The most common studies of pharmacokinetic interaction usually involve the metabolizing enzymes, mainly cytochrome P450. This enzyme plays an important role in phase I metabolizing processes that impart the metabolite with increased polarity compared with the parent compound. Cytrochrome P450 is a large family of related isoforms and those are responsible for most of the metabolism of drugs include CYP1A1, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5, and CYP4A (Table 1).[16]

The CYP1 family is responsible for activating carcinogenic aromatic amines and heterocyclic amines as well as drug metabolism. Aqueous and alcoholic extracts of *A. paniculata* (equivalent to 5mg/kg/day andrographolide) were reported to induce mouse hepatic cytochrome P450 isoforms CYP1A1 and CYP1B1 via significant increases in ethoxyresorufin *O*-dealkylase and pentoxyresorufin *O*-dealkylase activities, respectively.[18] Andrographolide (12.5-50 μM) extensively induced the expression of CYP1A1 mRNA in concentration-dependent manner comparable to the typical CYP1A inducers, including benz[α] anthracene, β-naphthoflavone, and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. It induced CYP1A2 less markedly and did not induce CYP1B1 expression.[19] In addition, 11, 12-didehydro-14-deoxyandrographolide (DHA) induced CYP1A1 mRNA expression, but neoandrographolide (Neo) and andrographiside (AS) did not show the induction. When co-treated with a CYP1A inducer (β-naphthoflavone, BNF), andrographolide and DHA showed a synergistic increase of CYP1A1 expression. Also, andrographolide demonstrated higher enhancing activity than DHA at the same concentration. On the other hand, Neo suppressed BNF-induced CYP1A1 expression while AS did

**TABLE 1.** Major drug metabolizing cytochrome P450 enzymes affected by *A. paniculata* and its major active components. (Adapted from reference 24, 47-49).

| Human CYP450 | Substrates | Drug class* | Comments |
|---|---|---|---|
| CYP1A1 | Granisetron | | Inducers : omeprazole, nimodipine, leflunomide, mexiletine, atorvastatin, flutamide, tobacco smoke |
| CYP1A2 | Amitriptyline, caffeine, clozapine, imipramine, paracetamol, tacrine, theophylline | | Inducers : omeprazole, dioxin, tobacco smoke. Inhibitors: furafylline, fluvoxamine |
| CYP1B1 | Theophylline, caffeine, 17β-estradiol | | Inhibitors: tamoxifen, doxorubicin, daunomycin, docetaxel, paclitaxel, mitoxantrone |
| CYP2C9 | Diclofenac, naproxen, phenytoin, piroxicam, tolbutamide, warfarin | Non-steroidal anti-inflammatory drugs | Inducers : barbiturates, rifampicin. Inhibitors: sulfaphenazole |
| CYP2C19 | Diazepam, mephenytoin, omeprazole, propanolol | Proton pump inhibitors | Inducers : barbiturates, rifampicin. Inhibitors: fluconazone |
| CYP3A4 | Alprazolam, amiodarone, amitryptyline, carbamazepine, cisapride, clarithromycin, cyclosporin, dexamethasone, erythromycin, ethinyl oestradiol, ketoconazole, midazolam, nifedipine, taxol, verapamil, warfarin | Statins, calcium channel blockers, immune modulators, macrolides, protease inhibitors, benzodiazepines | Inducers : carbamazepine, phenytoin, rifampicin, steroids, barbiturates. Inhibitors: ketoconazole, gestodene, grapefruit juice |

*A number of drugs in these drug classes are metabolized by the CYP450 isoform.

not modify the induction. Molecular docking analysis suggested that andrographolide and DHA increased binding affinity of BNF to mouse aryl hydrocarbon receptor ligand binding domain (AhR-LBD). However, the complex of mouse AhR-LBD and diterpenoid glycoside (Neo or AS) might not be appropriate for increasing binding affinity of BNF.[20] In addition, synergistic effect on CYP1A1 expression by andrographolide plus CYP1A inducer (3-methylcholanthrene) was observed *in vivo* only in polycyclic aromatic hydrocarbon (PAH)-responsive C57BL/6 mouse, but was not observed in PAH-nonresponsive DBA/2 mouse. This synergistic effect was found to be sex-dependent because the enhanced expression induced by andrographolide occurred in male C57BL/6 mice, but did not occur in intact or ovariectomized females, or in orchiectomized male mice. Furthermore, treatment with testosterone restored the effect in both ovariectomized females and orchiectomized male mice.[21]

*A. paniculata* extract also showed inhibitory effects on rat and human CYP1A2-dependent ethoxyresorufin-*O*-deethylation with $IC_{50}$ of 5.1 and 10.3 μM, respectively. This inhibition was categorized as non-competitive inhibition.[22] Andrographolide (60 μM) and DHA (15 μM) significantly reduced the CYP1A2 mRNA and protein expressions in HepG2 cells, a human hepatocellular carcinoma cell line. Moreover the ability of BNF to induce CYP1A2 expression was also reduced by both compounds.[23]

CYP2C subfamily is involved in the oxidation of xenobiotic and endogenous compounds. It metabolizes approximately 20% of therapeutic used drugs such as anticonvulsant agents, non-steroidal anti-inflammatory drugs, proton pump inhibitors, and the anticoagulant wafarin.[24-25] *A. paniculata* extract inhibited CYP2C both in rat and human liver microsomes with $IC_{50}$ of 3.86 and 16.16 µM, respectively with inhibition constant ($K_i$) values of 8.21 and 7.51 µM, respectively. The results indicated a mixed type inhibition.[22] Furthermore, an *in vivo* study showed significantly inhibitory effects of *A. paniculata* extract (equivalent to 5 and 25mg/kg/day andrographolide) and andrographolide (5 and 25 mg/kg/day) on rat CYP2C11 activity. Primary culture of human hepatocytes, treated with andrographolide (50 µM) or *A. paniculata* extract (containing 50 µM andrographolide) also showed significantly inhibitory effects on CYP2C9-dependent monooxygenase activity and mRNA expression.[26] The ethanol extract of *A. paniculata* exhibited significant inhibition on CYP2C19 with an $IC_{50}$ value of 91.7 µg/ml and a *Ki* value of 67.1 µg/ml with mixed-type inhibition. However, aqueous, methanol and hexane extracts as well as andrographolide showed negligible effect on CYP2C19.[27]

CYP3A subfamily, the most abundant of the human CYP isoforms, is localized in organs of particular relevance to drug disposition including gastrointestinal tract, kidney, and liver. It is involved in the metabolism of many therapeutic drugs.[28] *A. paniculata* extract showed a competitive inhibition on CYP3A4 in human liver microsomes with an $IC_{50}$ value of 34.1 µM and a $K_i$ value of 25.43 µM.[22] In human hepatocytes, andrographolide (50µM) and *A. paniculata* extract (containing 50µM andrographolide) significantly decreased CYP3A-dependent monooxygenase activity and mRNA expression. The extract was a more potent inhibitor of CYP3A activity than andrographolide, suggesting that beside andrographolide other components in the extract of *A. paniculata* may modulate the effect.[26] Another study revealed that andrographolide (60 µM) and DHA (15 µM) significantly inhibited CYP3A4 mRNA and protein expression in HepG2 cells. Both compounds decreased the ability of dexamethasone to induce CYP3A4 expression and enzyme activity. Furthermore, DHA inhibited CYP3A4 by binding and antagonizing to pregnane X receptor.[23] Study on the effects of andrographolide on the expression and metabolic activity of intestinal CYP3A4 in Caco-2 cells, human colon carcinoma cell line, demonstrated that andrographolide (1, 10, 100 µM) significantly down-regulated the mRNA and protein level of CYP3A4, and inhibited nifedipine oxidation and testosterone 6$\beta$-hydroxylation.[29]

The regulation of other CYP isoforms by *A. paniculata* extract and its active components has also been investigated. The inhibition of CYP2D6 mRNA and protein expressions in HepG2 cells,[23,30] showed weak inhibition of rat CYP2E1 while no significant effect on human CYP2E1[22,26] were reported.

## The effects of *A. paniculata* and its major active components on phase II metabolizing enzyme

Phase II drug metabolizing processes include sulfation, methylation, acetylation, glutathione conjugation, fatty acid conjugation and glucuronidation.[23] Glutathione S-transferase (GST) is one of the phase II metabolizing enzymes that catalyzes the conjugation of glutathione (GSH) with a variety of electrophilic xenobiotics and facilitates the excretion of conjugates. An investigation of the effect of *A. paniculata* on the expression of pi class of glutathione S-transferase (GSTP) in rat primary hepatocytes showed that the ethanol (25, 50 µg/ml) and ethyl acetate (25, 50 µg/ml) extracts as well as andrographolide (10, 20 µM) dose-dependently induced GSTP protein and mRNA expression via the phosphatidylinositol 3-kinase (PI3K)/Akt pathway.[31-32] Andrographolide significantly decreased GSH levels in HepG2 cells by molecular interaction and two major products, 14-deoxy-12-(glutathione-amino)-andrographolide and 14-deoxy-12-(glutathione-S-yl)-andrographolide were produced. The mechanism of the molecular reaction begins with Michael addition at $\alpha,\beta$-unsaturated lactone moiety (C-12) of andrographolide to form an anion intermediate. Subsequently, the allylic hydroxyl is eliminated from C-14 to form the final products.[33] Moreover the interaction of andrographolide with GSH was

found to modulate the effect of andrographolide on BNF-induced CYP1A1 mRNA expression in mouse hepatocytes.[34]

Uridinediphosphoglucuronosyltransferase (UGTs) catalyzes glucuronidation reaction which is an important metabolic pathway for many drugs and endogenous substances. In humans, 16 different UGT isoforms have been classified into either 1A or 2B subfamilies.[16] Investigation of the inhibitory potential of andrographolide and 9 derivatives towards UGT isoforms revealed that andrographolide, 14-deoxyandrographolide, 3-oxo-deoxyandrographolide, and 3-oxo-dehydroandrographolide exhibited the selective inhibition towards recombinant UGT2B7-catalyzed 4-methylumbelliferone (4-MU) glucuronidation and human liver microsome-catalyzed zidovudine (AZT) glucuronidation.[35] Accordingly, the possible herb-drug interactions between *A. paniculata* and clinical drugs mainly undergoing UGT 2B7-catalyzed metabolic pathway, such as opioid analgesics, NSAIDs, benzodiazepines, and AZT[36-37] should be of concern to healthcare practitioners.

**The effects of *A. paniculata* and its major active components on drug transporter protein**

P-glycoprotein (P-gp) is a well-known drug transporter protein that is highly expressed in the apical membrane of several pharmacologically important epithelial barriers such as the kidney, liver, intestine, and blood-brain barrier. It is involved in the efflux of drugs, drug conjugates and endogenous substrates and has an impact on the extent of drug absorption in the intestinal tract, distribution to the brain, and elimination by the liver and kidney.[17] Therefore, herbs that modulate P-gp may increase the risk of herb-drug interactions particularly drugs with narrow therapeutic indices such as warfarin and digoxin. Increase of protein and mRNA levels of membrane transporter P-gp in rats treated with 2 g/kg ethanolic extract of *A. paniculata* (containing andrographolide 53 mg/g and DHA 30 mg/g) was observed while those treated with 50 mg/kg andrographolide showed only a minor effect on P-gp.[38] In addition, andrographolide (100 µM) showed relatively weak inhibitory effect on P-gp mediated digoxin transport in MDR1-MDCKII cells (multidrug resistance protein 1-Madin-Darby canine kidney cells) whereas DHA exhibited significant inhibition (IC$_{50}$ = 77.80 µM) by competitively binding to the transport sites.[39]

**The interactions of *A. paniculata* and its major active components on clinical drugs**

According to the effects of *A. paniculata* and its major active components on various metabolizing enzymes as well as transporter protein *A. paniculata* and its major active components which may interact with other medicines used in conventional therapy. Data concerning interaction of *A. paniculata* with some therapeutic drugs have been reported.

Theophylline is a bronchodilator with a narrow therapeutic index ranging from 5 to 20 µg/ml of serum concentration. It is principally metabolized in the liver by CYP1A2 and CYP2E1.[40] The investigation on pharmacokinetic interactions of theophylline and *A. paniculata* extract or andrographolide in rats revealed that pretreatment with *A. paniculata* extract (1 g/kg) or andrographolide (154 mg/kg) for 3 consecutive days significantly increased the elimination of theophylline in rat blood and decreased the area under concentration-time curve (AUC) at low-dose theophylline administration (1 mg/kg). When high-dose theophylline (5 mg/kg) was given, the elimination half-life and mean residence time of theophylline were shortened by 14% and 17%, respectively in the andrographolide pretreated group. Conversely, in *A. paniculata* extract pretreated group significant reduction of elimination of theophylline and increase in dose-normalized AUC ratio (AUC/dose) were observed. This phenomenon suggested that besides andrographolide, some other components in *A. paniculata* may interact with theophylline and retard its elimination at high-dose theophylline administration.[41] Midazolam, a short-acting benzodiazepine, has anxiolytic, sedative, hypnotic, anticonvulsant, muscle relaxant, and amnestic effects. It is extensively metabolized in both liver and intestine via CYP3A4 and CYP3A5 to 1'-hydroxymidazolam and 4-hydroxymidazolam, which undergo rapid conjugation with glucuronic acid and are excreted into urine within 24 hours.[42-43] Pretreatment with

4 capsules of 250 mg *A. paniculata* three times a day (equivalent to 8.36 mg of andrographolide per day) for 7 days in 12 normal volunteers did not significantly change the mean pharmacokinetic parameters of oral midazolam (7.5 mg, single dose). However, *A. paniculata* affected the pharmacodynamics of oral midazolam by augmenting the effect of midazolam in lowering blood pressure and pulse rate.[44]

Warfarin, a widely used oral anticoagulant, has a relatively high elimination half-life (10-14 hr in animals and 40-46 hr in human).[45] It occurs as a pair of enantiomers (*R*- and *S*-warfarins). The principal metabolism of *R*-warfarin in humans is catalyzed by CYP1A2 to 6-and 8-hydroxywarfarin, by CYP3A4 to 10-hydroxywarfarin, and by carbonyl reductases to diastereoisomeric alcohols. *S*-warfarin is metabolized primarily by CYP2C9 to 7-hydroxywarfarin. The phase I metabolites are then conjugated by glucuronosyl and sulfotransferases.[46] The effects of Kan Jang tablet, a standardized fixed combination of extracts from *A. paniculata* and *Eleutherococcus senticosus* containing andrographolide 4.25 mg/tablet, on the pharmacokinetics and pharmacodynamics of warfarin were evaluated in rats. Kan Jang was applied to a pretreated group at a daily dose of 17 mg/kg of andrographolide (17-fold greater than the recommended human dose) for 5 days before a single dose administration of 2 mg/kg warfarin. The concentration of warfarin in the blood of this pretreated group was slightly higher than in the control group during the first 6-7 hr following administration of warfarin, and achieved the maximum value ($C_{max}$) earlier. However, $C_{max}$, elimination half-life and mean residence time of warfarin were almost the same in both groups. Furthermore, maximum prothrombin time ($PT_{max}$) and area under the curve prothrombin time versus time curve extrapolated to infinity ($AUC_{PT0-\infty}$) were not statistically significantly different between the control and pretreated groups. Consequently, the concomitant application of Kan Jang and warfarin did not produce significant effects on the pharmacokinetics and pharmacodynamics of warfarin.[45]

## CONCLUSION

*Andrographis paniculata* (Burm.f.) Wall. ex Nees (Fa-tha-lai-jone) has been one of the medicinal plants in The National List of Essential Drugs A.D.2013. It is used for treatment of non-infectious diarrhea and common cold. Its major constituent is a diterpene lactone, andrographolide. Many evidences have indicated the influence of *A. paniculata* and its major components towards drug metabolizing process via phase I and II metabolizing enzymes as well as drug transporter protein. Pharmacokinetic interactions can occur when *A. paniculata* is combined with drugs which are substrates of CYP1A1, CYP1A2, CYP1B1, CYP2C9, CYP2C19, CYP3A4, GSTP, UGTs, and P-gp. *A. paniculata* affected the pharmacodynamics of oral midazolam by augmenting its effects in lowering blood pressure and pulse rate, but no significantly pharmacokinetic interaction was observed. However, it is important to continue documenting the history of the use of *A. paniculata* through a multi-professional approach involving physicians, pharmacists and other healthcare practitioners which could help minimize the risk of drug interactions. In addition, be aware when *A. paniculata* is co-administrated with any drugs that have narrow therapeutic windows or affect the same receptors.

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