中草藥與西藥交互作用臨床證據之探討

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於2012持續教育

前言

- 俗語說：是藥三分毒，且不分中西
- 十八反藥歌、十九畏藥歌
- 妊娠禁忌藥歌、食物禁忌歌
- Drug-Drug Drug-Food Drug-Herbal
- 臨床重要的藥物交互作用

交互作用的定義

- The pharmacological or clinical response to the administration of a drug combination different from that anticipated from the know effects of the two agents when give alone

Ref:David S Tatro Drug Interaction Facts 1996

- The effect of one drug upon the organism's reactivity to another drug

Ellenhorm MJ. Stemad FA Problems of drug interactions J Am Pharm Assoc 1966

藥物交互作用的發生率

- 篩選500個病人的處方
  - 使用4個藥物時，有50%會發生藥物交互作用。
  - 使用超過8個藥物時，發生的機會為90%。

Weideman, R.A., bernstein, I.H.,Mekinney, W.P. Am J Health Syst Pharm. 56(15), 1524-29,1999

藥物交互作用的分類
Pharmacokinetic

- 使用一個藥物後而引起另一個藥物在吸收、分佈、代謝、排除上的改變。
  - 改變吸收速率或吸收量
    - Iron與 Tetracycline;Erythromycin 與Digoxin
  - 分佈：以藥物由結合處被取代較常見
    - Aspirin與 Warfarin;Digoxin與 Quinidine
  - 代謝：促進作用或抑制作用
    - Cimetidine -Theophylline;Rifampin Oral contraceptives
  - 排除：腎臟排除的競爭
    - Thiazide與 Metolazone; Probenecid 與penicillin

藥物交互作用的分類
Pharmacodynamic

- 藥物的併用造成同一受體(receptor)或生理作用的相加、加乘或拮抗，而使其效果比單獨使用降低或增加。
- Antagonistic
  - propranolol 與terbutlin; naloxone與 codeine
- Synergistic或Additive
  - thiazide與 metolazone; benzodiazepine與 analgesic

影響藥物交互作用的因素

- 代謝的速率
- 疾病狀態
- 病患的食物
- 病患的年齡或種族
- 藥物劑量

對骨骼有影響的藥物

- Corticosteroids
- Heparin
- Thiazolidinediones (TZD)
- SSRI’s
- PPI’s
- Loop diuretics

Cytochrome P450 System and Drug transporters
於交互作用的相關性

Cytochrome P450 System

- 位於肝臟細胞的endoplasmic reticulum，長時間給藥可刺激smooth endoplasmic reticulum membrane的增生
- Cytochrome P450為含有heme的enzyme 其還原態可吸收450的波長光線
- 已確知人類有50種以下的isozyme 其中11種與藥物代謝有關，主要的為CYP3A4,CYPP2D6,CYP1A2, CYP2C subfamily
- Cytochrome P450執行Phase I reaction、Phase II reaction, 對體內及體外的物質進行氧化代謝作用

影響Cytochrome P450的因素

1. Genetic factors
   - extensive metabolizer
   - poor metabolizer: CYP2C19 在亞洲人中有18-20%人 該enzyme無效
   - 白種人中有5-10%缺乏CYP2D6，無法將codeine由O-demethylation作用成morphine，而對codeine反應不好；亞洲人有2% ，阿拉伯人有1%
2. Individual factors
   - 年齡、營養、壓力、疾病(尤其是肝臟)、荷爾蒙、其他體內化學物質、生活型態(抽煙、喝酒)

影響Cytochrome P450的因素

3. Drug factors

- Dose, Duration, Dosing time, Sequence, Route, Dosage form Environmental factors
- 身體受特殊因素的影響使代謝　增加或減緩代謝速度
- 葡萄柚汁與藥物的交互作用：抑制CYP1A2及CYP3A4，增加藥物caffeine, cyclosporin, midazolam, trizolam, terfenadine, ethinyl estradiol, calcium channel blockers

Pharmacokinetic Mechanisms ～ altered metabolism ～

- cytochrome P450 isoenzymes (CYP)
  - about 40 different CYP enzymes are present in humans; CYP2A6, CYP2C9, CYP2D6, CYP3A4…… inhibitor, inducer, substrate of CYP enzymes
- Responsible for metabolism of :
  - most CCBs; most bzdS; most HIV protease inhibitors; most HMG-CoA-reductase inhibitors; cyclosporine; most non-sedating antihistamines; cisapride
- Present in GI tract and liver

Cytochrome P450 3A inhibitors and inducers

- Inhibitors :
  - ketoconazole
  - itraconazole
  - fluconazole
  - cimetidine
  - clarithromycin
  - erythromycin
  - grapefruit juice
- Inducers :
  - carbamazepine
  - rifampin
  - rifabutin
  - ritonavir
  - St. John’ s wort

Enzyme Inducer or Inhibitor
對藥物血中濃度的影響

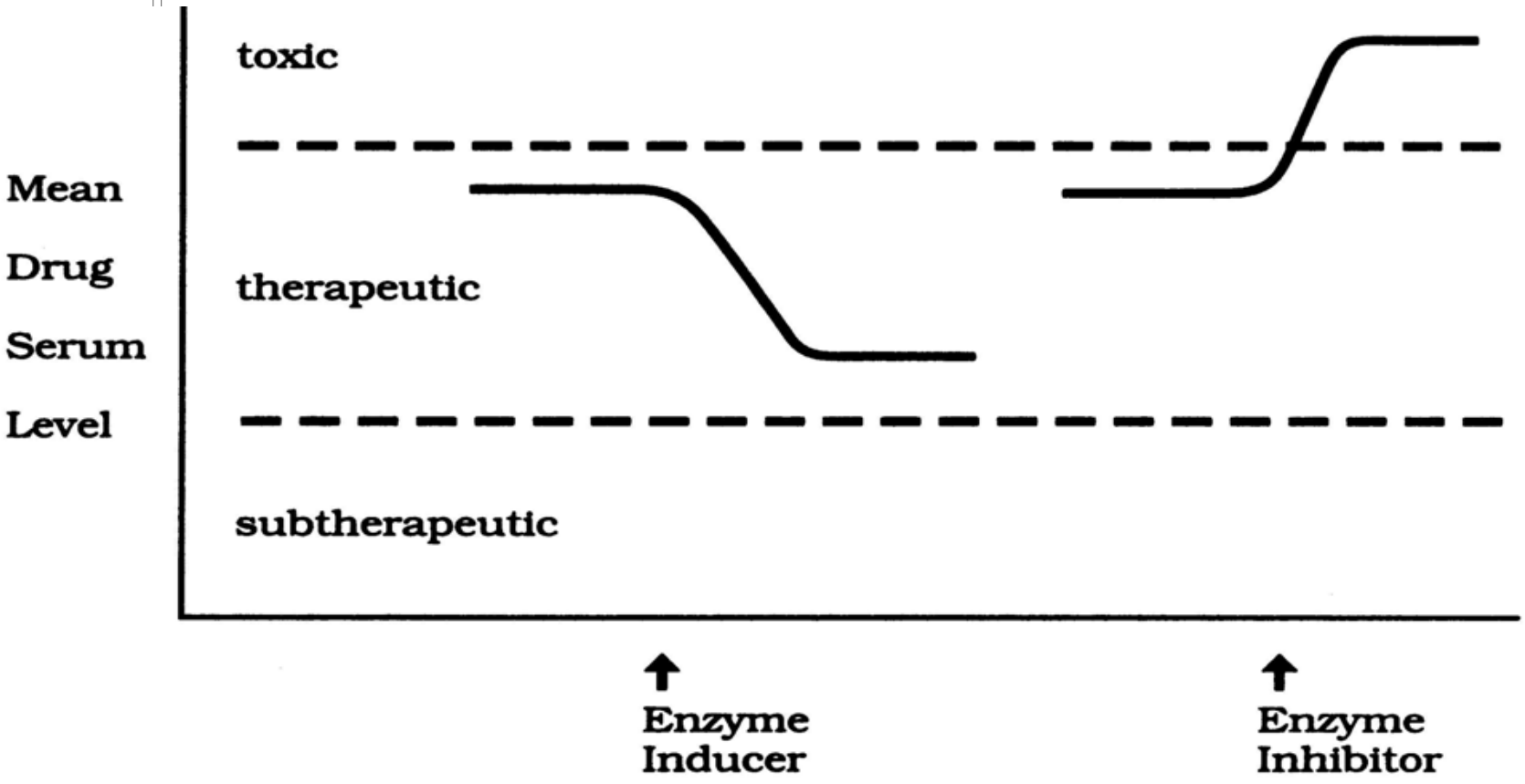

Diagram 1. Mean drug blood level response to an enzyme inducer or enzyme inhibitor

Cytochrome P450 3A

- Terfenadine $\xrightarrow{\text{CYP3A}}$ Fexofenadine
- Ketoconazole ⇨ ↓ CYP3A
  - ⇨ ↑ Terfenadine accumulates
  - ⇨ block potassium channels in the heart
  - ⇨ QT interval can be prolonged
  - ⇨ torsades de pointes can develop
- Fexofenadine has equal potency at the histamine receptor, but is more than 50 times less active in blocking potassium channels

Cytochrome P450 2D6

- absent in 7% of Caucasians, 1-2% non- Caucasians
- hyperactive in up to 30% of East Africans
- catalyzes primary metabolism of
  - codeine
  - many β-blockers
  - many tricyclic antidepressants
- inhibited by
  - fluoxetine
  - paroxetine
  - haloperidol
  - quinidine

Cytochrome P450 2C9

- absent in 1% of Caucasians and African-Americans
- primary metabolism of
  - most NSAIDs (including COX-2)
  - S-warfarin (the active form)
  - phenytoin
- inhibited by
  - fluconazole

Cytochrome P450 2C19

- Absent in 20-30% of Asians, 3-5% Caucasians
- primary metabolism of
  - Diazepam
  - Phenytoin
  - Omeprazole
- inhibited by
  - Omeprazole
  - Isoniazid
  - ketoconazole

Cytochrome P450 1A2

- induced by smoking tobacco
- catalyzes primary metabolism of
  - Theophylline
  - Imipramine
  - Propranolol
  - clozapine
- inhibited by
  - Many fluoroquinolone antibiotics
  - Fluvoxamine
  - Cimetidine

Influences on cytochrome activity

	1A2	2C	2D6	2E1	3A4
Nutrition	+			+	+
Smoking	+				
Alcohol				+	
Drugs	+	+	+		+
Environmental factors	+			+	+
Genetics		+	+		

J Am Acad Dermatol 2002;47:467-84.

Key factors in drug/herb interactions(1)

- 藥物－藥物；藥物－食物；藥物－中草藥：發生交互作用在於the CYP enzyme system and/or P-gp efflux pump 的成分為 substrate 或 inducer 或 inhibitor的競爭、干擾或誘導或抑制enzyme 或pump的活性所致的結果。

(1)substrate of one or several isoforms of CYP enzymes and/or efflux systems (P-gp, MRP and BCRP).

(2) an inducer of one or several CYP isoforms and/or efflux systems

(3) an inhibitor of CYP450 enzymes resulting in reduced activity of one or several isoforms of CYPs.

Key factors in drug/herb interactions(2)

- However, induction is a slow process, dependent on the rate of protein synthesis.
  - Expression of specific mRNA may be possible within a few hours, but functional expression and maturation of such proteins may require longer duration.
- In contrast, inhibition is more rapid and can produce results within a very short period of time, particularly if the inhibition is competitive in nature.

Pharmacokinetic Mechanisms ～ altered metabolism ～

- ↑ metabolism
  - ⇨ ↓ the serum level of object drug
  - ⇨ ↓ therapeutic activity
- onset：solw, may require up to 3 weeks
- enzyme inducer：

  phenobarbital、carbamazepine、phenytoin、rifampin 、cigarette smoking
- eg. warfarin ＋ phenytoin

  theophylline ＋ cigarette smoking

Role of CYP450 in drug – herbal interaction

- The CYP3A family of enzymes constitutes the most predominant phase-I drug metabolizing enzymes and accounts for approximately 30% of hepatic CYP and more than 70% of intestinal CYP activity.
- Moreover, CYP3A is estimated to metabolize between 50% and 70% of currently administered drugs (Watkins et al., 1987).

Pharmacokinetic Mechanisms ～ altered metabolism ～

- ↓ metabolism
  - ⇨ ↑ the serum level of object drug
  - ⇨ ↑ therapeutic activity
- onset：rapid, frequently within hours
- enzyme inhibitor：
  - allopurinol、amiodarone、chloramphenicol 、 cimetidine、ciprofloxacin、diltiazem、erythromycin、ketoconazole、omeprazole
  - eg. astemizole or terfenadine ＋ erythromycin ；
    theophylline ＋ cimetidine

Inhibitors, inducers and substrates of Cytochrome P450 enzymes

Isozyme	Substrate	Inhibitor	inducer
CYP2D6	Chlorpromazine Codeine Dextromethorphan Donepezil Fluoxetine Sertraline ……	Amiodarone Cimetidine Codeine Fluoxetine Paroxetine Quinidine……	Not affected by common inducers
CYP3A4	Amiodarone Astemizole Carbamazepine Cisapride Erythromycin Felodipine Omeprazole……	Cimetidine Erythromycin Fluoxetine Grapefruit juice Ketoconazole Quinidine Sertraline……	Carbamazepine Macrolides Phenobarbital Phenytoin Rifampin……

Role of efflux proteins on drug – herbal interaction

- Multidrug resistance (MDR) proteins play an important role in protecting cells against cytotoxic drugs (Borst et al., 2000).
- The multidrug resistance phenotype in tumors is associated with over expression of ATP binding cassette (ABC) efflux pumps termed MDR proteins. P glycoprotein (P-gp, MDR1, ABCB1) (Chen et al., 1986; Juliano and Ling, 1976; Ueda et al., 1987)

Role of efflux proteins on drug – herbal interaction

- Two other ABC transporters have also been demonstrated to participate in the multidrug resistance of tumors. These are multidrug resistance protein 1 (MRP1, ABCC1) and mitoxantrone resistance protein (MXR) or breast cancer resistance protein (BCRP or ABCG2) (Borst et al., 2000; Cole et al., 1992; Deeley and Cole, 1997; Gottesman and Pastan, 1993; Litman et al., 2001).

Coordinated function of efflux and metabolism

- Since HIV protease inhibitors, macrolide antibiotics, azole antifungals and herbals are substrates of same the metabolizing enzymes and transporters,
- herbal agents can adversely affect the course of HIV treatment and other opportunistic infections.
- In studies indicated that concomitant administration of erythromycin with SJW and/or ketoconazole can enhance erythromycin oral absorption
- Saint John's wort：CYP(s) substrate 3A4, 1A2, 2C9；P-gp substrate

P-gp and CYP(s)

中草藥交互作用主要因素

Drug	CYP(s) substrate	P-gp substrate
Carbamazepine	3A4, 2C8	－
Digoxin	－	＋
Theophylline	1A2	－
Saint John’ s wort	3A4, 1A2, 2C9	＋
Warfarin(抗凝血劑)	2C9, 1A2, 3A4	－
Simvastatin, Pravastatin	3A4	＋
Indinavir, Ritonavir, Saquinavir,lopinavir	3A4	＋
Nevirapine	2B6,3A4	－
Irinotecan(抗癌藥)	3A4, 3A5	＋
口服避孕藥	3A4	－
Methadone	3A4,2C8,2D6	－
Fexofenadine第二代抗組織胺	3A4	＋

中藥之配伍禁忌
七情－合用藥物間的相互作用

1. 單行：藥物單獨使用
2. 相須：兩種性能功效相似的藥物配伍應用，能互相協同可提高療效(知母配黃柏增加清熱效果)
3. 相使：兩種性能功效有某些相同的藥物配伍應用，以其中一藥為主，另一藥為輔 輔藥可提高主藥的療效(木香配黃連增強止瀉止痛效果)
4. 相畏：兩藥合用，一藥之毒副作用能被另一藥減少(生薑減低半夏之毒)
5. 相殺：兩藥合用，其中一藥能減輕另一藥之毒副作用(防風殺砒霜之毒)
6. 相惡：兩藥合用，能互相牽制，使藥物療效降低或消失 (生薑惡黃芩)
7. 相反：兩藥合用，能使藥物產生不良之毒副作用。(藜蘆反人參)

中藥毒性與副作用的來源

- 藥物本身即含有毒性成分（川烏、草烏）
- 藥物劑量因素（細辛）
- 給藥途徑或使用方式不當
- 藥物炮製處理不當（八寶散）
- 藥物的誤用（曼陀羅花當成曇花來泡茶）
- 不當藥物併用的交互作用（芸香科；陳皮 橘紅與西藥降血壓的交互作用）

中藥干擾 Digoxin血中濃度分析

Table 4 Herbal Products That May Interfere With Digoxin Level and Assays

Herb	Extent of Interference	Comments
Chan su	High	Active components (e.g., bufalin) cross-react with digoxin assay Monitoring free digoxin eliminates interference
Danshen	Moderate	Falsely increases (FPIA) or falsely decreases low levels (MEIA) of digoxin Monitoring free digoxin eliminates interference
Asian ginseng	Moderate	Falsely increases elevated (FPIA) or falsely decreases low (MEIA) digoxin level Monitoring free digoxin does not eliminate interference
Siberian ginseng	Moderate	Falsely increases elevated (FPIA) or falsely decreases low (MEIA) digoxin Monitoring free digoxin does not eliminate interference
Uzara root (diuretic)	NA	Increases effect with digoxin Interferes with digoxin assay

Adapted and reprinted, with permission, from Dasgupta A. Review of abnormal laboratory test results and toxic effects due to use of herbal medicines. Am J Clin Pathol 2003;120:127–37.

FPIA = fluorescence polarization immunoassay; MEIA = microparticle enzyme immunoassay; NA = not available.

臨床文獻證據之探討

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Evidence-based drug–herbal interactions

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MDR- and CYP3A4-mediated drug herbal interactions

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Clinical Evidence of Herb-Drug Interactions: A Systematic Review by the Natural Standard Research Collaboration

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Abstract: To evaluate the pharmacokinetics and adverse effects of medicinal herbs, as well as clinical evidence of herb-drug interactions. Electronic searches were conducted in multiple databases, including MEDLINE, EMBASE, the Cochrane Library, CINAHL, NAPRALERT, International Pharmaceutical Abstracts, CANCERLIT, CISCOM, and HerbMed. Search terms used included common names, scientific names, and synonyms for the herbs and their primary active constituents. Bibliographies of relevant articles were also searched by hand to obtain additional references. No restrictions were placed on language or quality of publications. All literature collected pertained to adverse effects, pharmacokinetics, and suspected or confirmed cases of herb-drug interactions. Over 80 herbs or botanicals (including plants, fungi, algae, and common constituents) were identified that had clinically significant interactions with prescription and over-the-counter drugs. Interestingly, herbs beginning with the letter "g" (garlic, ginger, ginkgo, and grapefruit) were among the herbs most commonly involved in herb-drug interactions. Drugs with anticoagulant/antiplatelet activity (e.g. warfarin, aspirin) were frequently implicated in herb-drug interactions, with documented interactions with over 30 herbs and herbal products. Because many herbs have demonstrated adverse effects on the liver, the potential for interaction with hepatotoxic agents (such as acetaminophen) is also significant. Clinical outcomes of reported herb-drug interactions ranged from mild to severe. Of note, fatalities (though rare) have occurred with concomitant ephedra and caffeine use. As herbal products (and dietary supplements in general) continue to grow in popularity, patients and health care providers should be vigilant of potential herb-drug interactions.

Keywords: Herbs, drugs, dietary supplements, interactions, pharmacokinetics, adverse effects.

Evidence for herbal–drug interactions

- “statin” drugs decrease the biosynthesis of coenzyme Q10 and adverse effects secondary to “statin” drugs may be due to the resultant decrease in tissue levels of coenzyme Q10 (Folkers, et al., 1990; Rundek et al., 2004).

- Thus, supplementation with coenzyme Q10 by patients on statin therapy may be beneficial.

Summary of St John's Wort (SJW) 聖約翰草 Interactions

- St John's wort may cause both pharmacokinetic and pharmacodynamic interactions. Pharmacokinetic interactions (lowering of plasma concentrations) arise when St John's wort is combined with drugs that are substrates of CYP3A4, CYP2E1 and CYP2C19, and/or P-glycoprotein.

Summary of St John's Wort (SJW) 聖約翰草 Interactions

- Among these, interaction with ciclosporin or antiretrovirals drugs may have serious clinical consequences. Hyperforin is the ingredient of St John' s wort responsible for P-glycoprotein and CYP induction.

Summary of St John's Wort (SJW) 聖約翰草 Interactions

- Pharmacodynamic interactions may occur when St John's wort is combined with drugs that enhance serotonin signalling in the brain. For example, St John's wort has been shown to cause serotonin syndrome when combined with serotonin reuptake inhibitors and serotonin receptor agonists.

St John's Wort Interactions

- **Anesthetic agents:**
- **Anticoagulants/antiplatelets: ↓ INR**
- **Antidepressants:**
  - **↑ SSRI & MAOI reuptake**，導致 serotonin syndrome or hypertensive crisis.
- **Benzodiazepines:增加BZD的代謝**
- **Digoxin:** decrease of digoxin levels by 25%
- **Estrogenic agents: SJW ↑ CYP 3A4活性.**
- **Cyclosporine: 受SJW影響降低血中濃度**

SJW Interactions

- **Cytochrome P450 substrates:**
  - Human studies have reported St. John's wort to induce CYP450 3A4 .
  - St. John's wort (hyperforin) has been shown to activate a regulator (pregnane X receptor) of 3A4 transcription and thereby induce expression of 3A4 in human liver cells .
  - There are mixed results regarding St. John's wort on other CYP450 isoenzymes .
  - St. John's wort has been shown to induce 1A2, 2C9, 2D6, 2C19, and 2E1 . Agents such as chemotherapeutic agents (irinotecan, etoposide, vinblastine, vincristine, vindesine), protease inhibitors (ritonavir, amprenavir), antifungals (ketoconazole, itraconazole), and many others should be avoided with St. John's wort.

SJW Interactions

- **HMG-CoA reductase inhibitors:**
  - 降低 simvastatin 血中濃度(but not pravastatin),
- **Imatinib (Gleevec®):**
  - increase the clearance
- **Irinotecan (Camptosar®):**
  - reduce irinotecan effectiveness
- **Methadone:長期使用SJW , ↓** methadone levels

SJW Interactions

- **Non-nucleoside reverse transcriptase inhibitors (NNRTIs): ↓ NNRTIs** plasma concentrations
- **Protease inhibitors: ↓** plasma concentrations
- **Tacrolimus (Prograf®):**
  - SJW decrease the levels of the immununosuppressant tacrolimus
- **Theophylline :**
  - SJW affect serum levels of theophylline or its metabolites

Ginkgo biloba–drug interactions

- G. biloba has been reported to cause spontaneous bleeding in patients who are generally healthy (Rowin and Lewis, 1996;Gilbert, 1997; Fong and Kinnear, 2003; Fessenden et al., 2001;Destro et al., 2005), possibly due to the antiplatelet effects of the ginkgolide B component (Rosenblatt and Mindel, 1997; Meisel et al., 2003).have been reported with aspirin, ibuprofen,and warfarin ◦

Ginkgo biloba – drug interactions

- Case report of interactions of possible interactions with G. biloba and trazodone has been reported. the patient lapsed into a coma, which was reversed immediately upon intravenous administration of 1 mg flumazenil, suggesting a link with the GABAergic system.
- G. biloba may act as an antagonist of gamma-aminobutyric acid (GABA) activity at benzodiazepine binding sites (Huang et al., 2004). Therefore, its use in patients taking drugs which are ligands for benzodiazepine binding sites should be avoided.

Ginkgo biloba – drug interactions

- There is a case report of a possible interaction with G. biloba and valproate.
- In one report, two separate patients suffered seizures when G. biloba and valproate sodium were administered concomitantly (Granger, 2001).

Ginkgo biloba – drug interactions

- **Thiazides:**
  - taking a thiazide diuretic and *Ginkgo, it has been* found to decrease systolic and diastolic blood pressure in healthy volunteers [531,532].
- Caution is warranted with concomitant use.

Ginkgo biloba – drug interactions

- Warfarin
  - Signs and symptoms of interaction：
    - Brain hemorrhage (intracerebral)
  - Mechanism：
    - Increased anticoagulation (Dasgupta, 1990)
- Aspirin
  - Signs and symptoms of interaction：
    - Spontaneous bleeding
  - Mechanism：
    - Increased anticoagulation (Chavez and Chavez, 1998; Rosenblatt and Mindel, 1997)

Ginkgo biloba – drug interactions

- Acetaminophen、caffeine and ergotamine
  - Signs and symptoms of interaction：
    - Brain hemorrhage (subdural)
  - Mechanism：Unknown
- General anesthetic
  - Signs and symptoms of interaction：
    - Risk of excess bleeding post operation
  - Mechanism：Blood thinning action of herb (Kaye et al., 2000)

Ginkgo biloba – drug interactions

☐ Fluoxetine (Prozac®):

- G*inkgo has been used to treat erectile* dysfunction [533]，and may interact with other agents used in the management of vascular erectile dysfunction.
- *Ginkgo has also been* reported to relieve sexual dysfunction associated with the selective serotonin reuptake inhibitor (SSRI) fluoxetine (Prozac®) [534]
  -

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Ginkgo biloba – drug interactions

☐ Nifedipine (Adalat®, Procardia®):

- **The effects of *Ginkgo leaf*** extract on the pharmacokinetics and pharmacodynamics of nifedipine, were studied in healthy volunteers [535,536].
- The maximal plasma nifedipine concentrations in two subjects were approximately doubled by *Ginkgo, and they had more* severe and longer-lasting headaches with *Ginkgo than without*
- *Ginkgo. Oral administration of nifedipine with Ginkgo also increased* heart rate over *Ginkgo alone.*

Warfarin–Herb drug interactions

- coenzyme Q10 interactions
- ginger interactions
- danshen interactions
- dong quai interactions
- G. biloba interactions
- garlic interactions
- American ginseng (Panax quinquefolium L.)interactions
- Asian ginseng (P. ginseng) interactions
- green tea interaction
- soy interactions
- omega fatty acid interactions
- saw palmetto interactions
- vitamin C interactions
- vitamin E interactions
- St. John's wort–drug interactions

Dietary supplement：Danshen 丹蔘

- Other drugs：

  Digoxin、Furosemide、Captopril

- Signs and symptoms of interaction：

  Increased INR

- Mechanism：

  Additive effect due to coumarin content in danshen

Goji (*Lycium spp.), Wolfberry*
枸杞

- 枸杞提取物高劑量可能引起警覺性，在睡前服用可能會與睡眠相互干擾，也可能會引起噁心和嘔吐。
- Interaction：Goji fruit was shown to elevate international normalized ratio (INR) in a patient stabilized on warfarin.

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Dietary supplement：Dong quai 當歸

- Other drugs：Digoxin、furosemide
- Signs and symptoms of interaction：
  - 2-fold increase in prothrombin time and INR
- Mechanism：
  - Possible inhibition of platelet activity by dong quai

Garlic 大蒜 – drug interactions

- Adverse Effects
  - Excessive use has been associated with spontaneous epidural hematoma [474].
  - Potential reactions associated with oral garlic use
    - bleeding (multiple case reports and a scientific basis)
    - and hypoglycemia (likely not clinically significant);
    - topical exposure may elicit dermatitis or burns (multiple reports).

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Garlic 大蒜 – drug interactions

- There have been an ectodal reports of elevated international normalized ratios (INRs) and prothrombin times in warfarin-stabilized patients after taking garlic [488].
- In a recent crossectional, point-of-care survey of 1818 patients, 25 cases were identified as potential clinically significant interactions between garlic and anticoagulants/antiplatelets [10].

Current Drug Metabolism, 2008*, Vol.9, No. 10*

Garlic 大蒜 – drug interactions

- Warfarin (anticoagulant)
  - Interaction ：Additive blood thinning effects

    possible inhibition of platelet aggregation
  - Comment：Possible of spontaneous bleeding

    (Burnham, 1995; Rose et al., 1990)
  - Garlic should be used cautiously in patients taking warfarin or other anticoagulants.

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Garlic 大蒜 – drug interactions

- General anesthetic
  - Interaction ：Blood thinning action of garlic
  - Comment：Risk of excess bleeding post-operatively (Kaye et al., 2000)
- Saquinavir (protease inhibitor)
  - Interaction：Herb reduces blood level drug, lowers drug effect
  - Comment：May cause failure of therapy in AIDS (Piscitelli et al., 2002a,b)

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Saw Palmetto 鋸棕櫚（鋸草）

- Saw palmetto (*Serenoa repens/Sabal serrulata*) Extra：FDA 列為保健食品,純粹天然粹取,類同Propecia, Extra的作用在於抑制雄性睪固酮轉換成DHT.
- In the early 1900s, men used the berries to treat urinary tract problems.
- Today, the primary use to treat benign prostatic hyperplasia (BPH), a noncancerous enlargement of the prostate gland. Researchers aren't sure exactly how saw palmetto works, but it contains plant-based chemicals that may be effective for BPH.
- Researchers think that saw palmetto may affect the level of testosterone in the body, and perhaps reduce the amount of an enzyme that promotes the growth of prostate cells.

Saw Palmetto 鋸棕櫚 – Possible Interactions

- Finasteride (Proscar)
  - saw palmetto may work similarly to Proscar.
- Antiplatelet and anticoagulant drugs (blood-thinners)
  - Saw palmetto may affect the blood's ability to clot, and could interfere with blood-thinning drugs, including:
  - Warfarin (Coumadin) 、Clopidogrel (Plavix) 、Aspirin
- Oral contraceptives and hormone replacement therapy
  - -Saw palmetto may reduce the number of estrogen and androgen receptors, and thus have hormone like effects.

Ref: http://www.umm.edu/altmed/articles/saw-palmetto-000272.htm#

Ginseng (Asian Ginseng) – Drug Interactions

- Asian (or Korean) Ginseng (roots of Panax ginseng) is marketed for a wide range of indications, which include erectile dysfunction, cancer prevention, enhanced physical function and improved cognitive functions.
- 臨床研究，人參對CYP亞型，包括CYP3A4的，CYP1A2，CYP2E1和CYP2D6沒有影響。僅老年人服用會輕微抑制 CYP2D6 的代謝

Ginseng (Asian Ginseng) – Drug Interactions

- Other drugs：
  - Antidiabetes drugs：增加降血糖作用
  - Digoxin：干擾Digoxin檢測, 增加中毒風險
  - Warfarin：降低Warfarin療效
    - 西洋參(American ginseng，其他人參?)
  - Phenelzine sulfate ：頭痛、失眠、震顫

Licorice (*Glycyrrhiza glabra*) - Drug Interactions

- Adverse effects from glycyrrhizin are primarily a result from hormonal and electrolyte disturbances. Possible effects include hypokalemia, hypernatremia, and metabolic alkalosis.
- Interaction：
  - **Cardiac glycosides**
  - **Corticosteroids**:
  - Licorice has been shown to induce and inhibit cytochrome P450 2B6, 2C9, and 3A4

Liquorice **- drug interaction**

Liquorice (Glycyrrhiza glabra) 甘草		
Drug name	Results	comments
prednisolone	Glycyrrhizin decreases plasma clearance, increases AUC, increases plasma concentrations prednisolone	11-dehydrogenase converts endogenous cortisol to cortisone; orally administered glycyrrhizin is metabolised mainly to glycyrrhetinic acid
Hydrocortisone	Glycyrrhetinic acid potentiates of cutaneous vasoconstrictor response	Glycyrrhetinic acid is a more potent inhibitor of 5-,5-reductase and 11-dehydrogenase than is glycyrrhizin.

Liquorice **- drug interaction**

Liquorice (Glycyrrhiza glabra) 甘草		
Drug name	Results	comments
Oral Contraceptives	Hypertension, oedema, hypokalaemia.	Oral contraceptives use may increase sensitivity to glycyrrhizin acid. Women are reportedly more sensitive than men to adverse effects of Liquorice.

Papaya 番木瓜 (papain木瓜素)

- **Anticoagulants/antiplatelets: An interaction between papain -** warfarin has been proposed
- ↑ INR

Psyllium(洋車前子)-drug interaction

- Psyllium remains predominantly in the gut as a "bulk" agent. It is somewhat resistant to fermentation, and is passed largely unchanged through the gastrointestinal tract [975,976].
- It has significant "water-holding" capacity due to its high hemicellulose content [977]. Onset of action is 12-24 hours; full effect may take 2-3 days

Psyllium(洋車前子)-drug interaction

- **Anticoagulants/antiplatelets**:
- **Antidepressant agents**:
- **Cholestyramine (Questran®)**
- **Lithium**:
- **Carbamazepine**:
- **Digoxin**:
- **Orlistat (Xenical®)**

Yohimbine - drug interaction

- Alpha-adrenergic agents: Yohimbine is an alpha-adrenergic blocker, and has been reported to antagonize the effects of clonidine
- MAOI：contraindicated，due to an increased risk of hypertensive crisis.
- Opiates:increase or decrease naloxone-precipitated opiatewithdrawal symptoms
- Physostigmine: associated with anxiety, agitation, restlessness, and chest pain

Tetrandrine 粉防已碱

- Dietary supplement：防己科植物粉防己根,頭花千金藤塊根,毛葉轮环藤根,蝙蝠葛藤茎.
- 臨床用途：镇痛，肌肉鬆弛，抗過敏，抗心律不整，抗菌，抗腫瘤，降壓，抗肝硬化、矽肺病、類風溼性關節炎 。

Tetrandrine 粉防己碱

- Signs of interaction and mechanism：
  - Its vasodilative effect is due to inhibition of the L-type calcium channels (51) and possible competition with other calciumchannel blockers (52).
  - Tetrandrine lowers plasma glucose and causes hepatotoxicity and renal toxicity (53).

Tetrandrine 粉防己碱

- a bis-benzylisoquinoline alkaloid, is a calcium channel blocker.
- It has anti-inflammatory, immunologic and antiallergenic effects. It inhibits the degranulation of mast cells. It has a "Quinidine like" anti-arrhythmic effect.
- It has vasodilatory properties and can therefore reduce blood pressure.[2] Tetrandrine may have potential use for the treatment of liver disease[3] and liver cancer.[4][5][6] Tetrandrine has potential therapeutic value to prevent excess scarring/fibrosis in conjunctiva following trabeculectomy or in patients with severe conjunctival inflammation.[7] Tetrandrine has anti-inflammatory and anti-fibrogenic actions, which make tetrandrine and related compounds potentially useful in the treatment of lung silicosis, liver cirrhosis, and rheumatoid arthritis.[8]

Kava 卡瓦 胡椒

- 英文名 **Radix Piper metystici**
- 學名 ***Piper methysticum*** **Forst**
- 產地 **Southern pacific.** 南太平洋島嶼。
- **Methoxyyangonin(**甲氧基醉椒素**), one of the kavalactones(**卡瓦內酯**), is a reversible MAO-B inhibitor.**
- **Kavalactones can potentiate $GABA_A$ and produce calming effect (**鎮靜作用**).**
- 用於治療焦慮，憂鬱，失眠症。
- **Inhibits CYP2E1, antagonizes dopamine effects. And interact like BZD.**

Kava **Toxicity & Cautions**

- **Pipermethystine contained in stems and leave can be toxic to the liver.**
- **Flavokavain B found in the rhizoma may contribute to the toxicity effect.**
- **Kava has been reported to cause liver damage, including hepatitis and liver failure .**
- **Kava has been associated with several cases of dystonia (肌張力不全症)，異常的肌肉痙攣或不自主肌肉運動.**

Kava **Toxicity & Cautions**

- **Kava may interact with several drugs, including drugs used for Parkinson's disease.**
- **Long-term and/or heavy use of kava may result in scaly, yellowed skin. (鱗屑，泛黃的皮膚)**
- **Kava has been reported to cause drowsiness. Avoid driving and operating heavy machinery while taking kava.**
- **Do not use in case of having surgery or during pregnancy or during breast feeding.**

Common Herb-drug Interactions

Herb	Drug or Drug Class	Interaction or Other Comments
Comfrey 紫草	Phenobarbital	增加紫草代謝 Pyrrolizidine alkaloids (PAs) ,具嚴重肝毒性
Danshen 丹參	Anti-coagulant or platelet agents, Digoxin.	增加出血及Digoxin 副作用
Echinacea 紫錐花	Amiodarone statins, fibrates, niacin	延長 QT interval. 增加肝功能異常的風險
Ephedra 麻黃屬植物	Antidiabetes drugs Class 1A & class Ⅲ抗心律不整藥 β blocker MAO inhibitors	增加血糖值, 降低血糖藥的療效 延長 QT interval. 降低β blocker療效,導致高血壓與心律不整 導致高血壓

Common Herb-drug Interactions

Herb	Drug or Drug Class	Interaction or Other Comments
Ginseng 人蔘	Antidiabetes drugs Digoxin Warfarin Phenelzine sulfate	增加降血糖 干擾Digoxin檢測, 增加中毒風險 降低Warfarin療效 頭痛、失眠
St. John's wort 聖約翰草	Digoxin, Warfarin, Indinavir, Simvastatin, Theophylline, Class1A-3 抗心律不整藥. Cyclosporine, Clopidogrel Paroxetine	降低Digoxin, Warfarin, Simvastatin 等藥品血中濃度或療效. 增加Cyclosporine的代謝, 降低濃度 增加Clopidogrel療效與出血風險 噁心、嗜睡、精神不集中

Common Herb-drug Interactions

Herb	Drug or Drug Class	Interaction or Other Comments
Hawthorn 山楂	Digoxin Calcium-channel blockers or nitates	增加 Digoxin 的作用 增加血管舒張作用
Licorice 甘草	Spironolactone	增加 Spironolactone 作用
Saw palmetto	Anti-coagulant or platelet agents,	增加出血的風險
Soy milk 水飛薊	Warfarin	降低 Warfarin 的藥效
Garlic 大蒜	Aspirin, clopidogrel, warfarin, or heparinoid drugs	增加出血的風險

Herbal Products to Avoid in Patients with Cardiovascular Disease

Herb	Cardiac Adverse Effect of interaction
Alfalfa 紫花苜蓿	Increases bleeding risk with Warfarin
Aloe vera蘆薈	Hypokalemia causing digitalis toxicity and arrhythmia
Dong quai 當歸	Increases bleeding risk with Warfarin
Bilberry越橘(果實	Increases bleeding risk with Warfarin
Butcher's broom 金雀花	Decreases effects of alpha-blockers
Capsicum辣椒	Increases blood pressure (with MAOI)
Fenugreek 葫蘆芭	Increases bleeding risk with Warfarin, hypoglycemia
Fumitory 延胡索	Increases bleeding risk with Warfarin

Herbal Products to Avoid in Patients with Cardiovascular Disease

Herb	Cardiac Adverse Effect of interaction
Garlic 大蒜	Increases bleeding risk with Warfarin
Ginger 薑	Increases bleeding risk with Warfarin
Ginkgo 銀杏	Increases bleeding risk with Warfarin, aspirin or COX-2 inhibitors, Potential risk of seizures.
Ginseng 人蔘	Increases blool pressure Decreases effects of Warfarin hypoglycemia
Gossypol 棉子酚 棉子中黃色毒性物質	Increases effects of diuretics Hypoglycemia

Herbal Products to Avoid in Patients with Cardiovascular Disease

Herb	**Cardiac Adverse Effect of interaction**
Green tea 綠茶	Decreases effects of Warfarin (含有 Vitamin K)
Hawthorn 山楂	Potentiates action of cardiac glycosides and nitrates
Irish moss 鹿角菜 珊瑚草	Increases effects of antihypertensive
Kelp 海藻	Increases effects of antihypertensive and anticoagulant agents.
	Increases effects of antihypertensive

替代療法交互作用問題諸多 我們(藥師)應如何做?

- 持續研修中草藥與藥物、食物間的文獻資料報告
- 詢問病人可能在服用的西藥、中草藥或保健食品
- 提供最適當的產品建議(recommend the best products)
- 當急性或嚴重性疾病或不適症狀時，不宜建議使用中草藥
- 中草藥應避免與治療濃度狹窄的藥物併用,例如：
  - warfarin, cyclosporin, digoxin, HIV protease inhibitors, theophylline, carbamazepine

『用藥安全』的重點觀念

F Sjoqvist (1991)

問題不在於不安全的藥物

而在於不安全的使用藥品

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