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Herbal product–drug interactions mediated by induction

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Despite their common use, it is not widely recognized that herbal medicines can alter the efficacy of coadministered prescription drugs. Constituents in herbs interact with nuclear receptors to enhance metabolizing enzyme and/or transporter activity leading to reduced drug concentrations. Although St John's wort was the first and most frequently reported source of induction-style herb–drug interactions, this knowledge has not yet changed its current availability. This type of interaction is likely to be relevant to other herbal products. Caregivers need to be aware of the issues and options for therapeutic management.

An estimated 5–20% of the general public use herbal medicines, resulting in global annual sales of £35 billion (€50 billion, US$60 billion) [1, 2]. Up to 43% of individuals taking herbals were also taking a prescription drug or an over-the-counter drug [3]. Public interest in herbal products has developed because these substances come from natural sources, rather than being synthetic chemicals [4, 5]. They are sold in a variety of commercial outlets and are displayed in plain view, together with a number of relatively innocuous substances, including vitamins and minerals, giving the impression of uniform product safety and effectiveness.

Herbal products fall under different regulations from pharmaceuticals and are considered in the same regulatory category as dietary supplements, foods and nutrients. Yet many potent medications and toxic substances are derived from plants. Herbal products can be purchased without the consultation of a licensed healthcare professional in most North American and European countries. Moreover, herbals are often used for less than specific indications and are not subject to standard pharmaceutical criteria for safety. Once sold on the market, regulatory agencies need to act on sufficient solid scientific reports of a healthcare concern to restrict herbal product availability and usage. Based on current public perceptions, many patients are unlikely to consider that herbal self-medication carries risks or is associated with drug interactions and are therefore not likely to tell their healthcare professional of their use [6, 7]. Conversely, healthcare professionals are not accustomed to asking their patients about their consumption of herbal medicines [8, 9]. There is thus a lack of awareness in the potential for herbal products to cause undesirable clinical outcomes. Unfortunately, this occurs despite ample evidence that certain herbals can dramatically change the disposition and action of some frequently prescribed or essential medications, sometimes with profound adverse consequences. In this report, we address the phenomenon of herbal product-mediated enhancement of drug clearance mechanisms responsible for inactiva-

tion or elimination of a broad range of medications and its clinical impact. We focus particularly on certain herbal products that are convincingly responsible for herb–drug interactions, especially St John's wort.

Induction

Induction is a term used to describe a physiological adaptive response to continued xenobiotic exposure. It is characterized by enhanced gene transcription and/or translation, stabilized messenger ribonucleic acid, or inhibited protein turnover. The end result can be increased amounts of proteins that determine drug disposition, such as metabolic enzymes or transporters. The dose of the inducer determines its cellular concentration and hence the extent of induction. The resulting clinical effects usually start within a few days of repeated administration. After withdrawal of the inducer, reversal is generally complete within 1 week.

Case reports of reduced exposure and reduced degree and/or duration of drug response have often served as important stimuli for formal study of herbal–drug interactions [10]. A common *in vivo* method uses a drug probe that is a relatively safe substance inactivated or eliminated primarily by a single metabolic process (e.g. midazolam and cytochrome P450(CYP)3A4) or transport process (e.g. fexofenadine and P-glycoprotein). Increasingly popular is the use of probe 'cocktails' that determine the activities of multiple eliminating pathways on a single occasion. The probes are administered before and then after a suitable treatment period with a particular herbal product to examine their effects on clearance of the probe.

The molecular mechanisms that govern the inductive response are well established and *in vitro* tools are available to predict whether herbal products or their chemical constituents might cause a clinically important drug interaction. The most prominent mechanisms for induction are ligand-dependent transcriptional activation of nuclear receptors, such as the pregnane X (PXR), constitutive androstane (CAR) or aryl hydrocarbon receptors (AhR). Convenient cell-based screening assays for activation of nuclear receptors are routinely used. Further investigations in the cultured primary human hepatocyte model are performed to confirm induction of gene expression.

St John's wort

Treatment of depression is the indication for 15% of all herbal medicine use and St John's wort represents the most commonly purchased herbal product for this condition [11]. Case reports of misadventures with this popular product first focused public attention on the clinical importance of herb–drug interactions (Table 1). In the first case, St John's wort reduced blood ciclosporin concentrations sufficiently to cause acute heart transplant rejection [12]. Since measurement of ciclosporin concentrations is part of routine clinical practice, the pharmacokinetic basis for this adverse effect rapidly became apparent. Many cases of St John's wort–ciclosporin interactions after organ transplantation were reported over the next 2 years [13]. St John's wort was also shown to reduce plasma indinavir concentrations, resulting in an increased HIV load [14]. In both cases, the mechanism of the interaction was activation of the pregnane X receptor [15], followed by induction of the drug-metabolizing enzyme CYP3A4, which is involved in the oxidative metabolism of an estimated 50% of all medications, and the efflux drug transporter P-glycoprotein [16, 17].

St John's wort has become by far the most commonly documented herbal product involved in drug interactions, 79% of all case reports [18]; more than 270 publications address this topic. Based on induction of CYP3A4 and P-glycoprotein, St John's wort would be expected, and in some cases has been shown, to alter the disposition of other essential medications, including certain cytostatic drugs (doxorubicin, etoposide, paclitaxel, vinblastine), cardiovascular drugs (amiodarone, digoxin), HIV protease inhibitors (nelfinavir, ritonavir, saquinavir) and immunosuppressants (sirolimus, tacrolimus). Furthermore, case reports and formal clinical investigations have shown that St John's wort caused induction of other drug-metabolizing enzymes, including CYP2C9 (potential loss of efficacy of warfarin and phenprocoumon), CYP2C19 and CYP1A2 (potential loss of efficacy of theophylline). On the basis of its promiscuous effects on a number of key drug disposition genes, St John's wort could in principle affect the actions of about 80% of all medicines.

Given the extent of documentation, it is surprising that no cautionary statement indicating concern about drug interactions is generally found on bottle labels for St John's wort. Although it is cited in about 55 drug product monographs to cause drug interactions, no intervention by a licensed healthcare professional (pharmacist) is required at the time of purchase. Perhaps warning labels, such as those found on cigarettes, stating 'Self-care at own risk' would be appropriate. How much information is needed before there is adequate action? At a minimum, removal from general retail stores, storage behind the counter in pharmacies and consultation with the pharmacist before purchase would be appropriate for St John's wort.

Table 1
In vivo and *in vitro* studies involving induction by herbals

Herbal product	Clinical studies Drugs affected	Induced genes
Hypericum perforatum (St John's wort)	Ciclosporin [12], indinavir [14], ritonavir, omeprazole [19], digoxin [20], imatinib [21], oral contraceptives [22], sirolimus, tacrolimus [23], warfarin [24], theophylline [25]	CYP3A4, P-glycoprotein, CYP2C9, CYP2C19, CYP1A2, CYP2E1
Echinacea purpurea or *angustifolia*	Midazolam [26]	CYP3A4
Allium sativum (garlic)	Saquinavir [27]	MDR1
Ginkgo biloba	Omeprazole [28]	CYP2C19
Panax quinquefolius (American ginseng)	Warfarin [29]	CYP2C9
Herbal product	***In vitro*/preclinical studies Experimental system**	**Result**
Hypericum perforatum (St John's wort) [15]	Nuclear receptor activation assay Cultured human hepatocytes	PXR activation CYP3A4 induction
Artemisia capillaris, *Gardenia jasminoides* Ellis, *Rheum officinale* Baill, and *Scutellaria baicalensis* Georgi (Yin Zhi Huang) [30]	Nuclear receptor activation assay Mouse model	CAR activation CYP2B induction
Commiphora mukul (Guggulipid) [31, 32]	Nuclear receptor activation assay Mouse model	PXR and CAR activation CYP2B and CYP3A induction
Artemisia capillaris [33]	Nuclear receptor activation assay Cultured human hepatocytes	PXR activation CYP2B6, CYP3A4, and P-glycoprotein induction
Piper methysticum (kava kava) [34]	Nuclear receptor activation assay Cultured human hepatocytes	PXR activation CYP3A4 induction
Schisandra chinensis Baill (Wu Wei Zi) [35]	Nuclear receptor activation assay Cultured human hepatocytes	PXR activation CYP3A4 induction
Glycyrrhiza uralensis Fisch (Ging Cao) [35]	Nuclear receptor activation assay Cultured human hepatocytes	PXR activation CYP3A4 induction
Evodiae fructus [36]	Mouse model	CYP1A2 induction
Evodia rutaecarpa [37]	Mouse model	CYP1A2 induction
Panax ginseng [38]	Nuclear receptor activation assay	AhR activation
Glycyrrhiza glabra (liquorice root) [38]	Nuclear receptor activation assay	AhR activation
Harpagophytum procumbens (devil's claw) [38]	Nuclear receptor activation assay	AhR activation
Ginkgo biloba [38, 39]	Nuclear receptor activation assay Rat model	AhR activation CYP1A, CYP2B, and CYP3A induction
Actaea racemosa (black cohosh, previously *Cimicifuga racemosa*) [38]	Nuclear receptor activation assay	AhR activation

Other herbal medications

Accumulating evidence for St John's wort as an important cause of variability in drug response and morbidity has promoted investigations aimed at identifying similar actions of other herbal products. *In vivo* screening has shown that a variety of commonly available herbal products, such as *Echinacea* and garlic, can induce certain drug-metabolizing enzymes and transporters. Moreover, *in vitro* and preclinical tests have shown that several other herbal products, including *Artemisia*, kava

kava and Guggulipid, are important transcriptional activators of nuclear receptors and/or inducers of gene expression.

General comments and recommendations

Many patients will consider taking herbal medications. It is therefore important that healthcare professionals are aware of the issues and possible options for therapeutic management. Effective regulation of the manufacture, sale, or contents of herbal products is often lacking. Hence, on occasion, herbal products are adulterated with potent chemicals. Mostly, they have not been assessed for drug interactions. We make the following recommendations for the future use of herbal products:

- The use of herbal products should be discouraged, especially of those for which there is no scientific or clinical safety information, except under the guidance of a qualified prescriber.
- Patients who want to use herbal products should be advised about the potential for adverse effects and interactions, and close monitoring for potential deleterious effects is warranted.
- Prescribers should be alert to abrupt alteration or persistent unpredictability in medication efficacy as a possible consequence of the use of herbal products.
- Rather than altering the drug regimen, it may be advisable to take a careful dietary history and consider safer alternatives to herbal products.
- Withdrawal of a chronically administered herbal product that acts as an inducer in a patient stabilized on effective drug therapy can result in untoward pharmacological or toxic effects, owing to increased drug concentrations as metabolizing enzyme activities fall; herbal products with inducing properties should be withdrawn gradually, with careful monitoring.

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