Pharmacokinetic interactions between antiretroviral drugs and herbal medicines

Pharmacokinetic interactions between herbal medicines and antiretroviral drugs may increase the risk of toxicity or antiretroviral treatment failure. This review highlights known and potential interactions between antiretroviral drugs and commonly used herbal medicines.

Antiretroviral therapy has improved the prognosis of patients with human immunodeficiency virus (HIV) infection (Palella et al, 1998). Currently, antiretroviral therapy is the only treatment that has demonstrated efficacy for HIV. However, herbal medicines are widely used by HIV patients to complement conventional therapy. In a cross-sectional study in the UK, 61% of patients on antiretroviral therapy had used herbal medicines or supplements (Ladenheim et al, 2008) while in a South African study, 30% of patients admitted herbal medicine use (Peltzer et al, 2008). In western countries, commonly used herbal medicines include garlic, echinacea, aloe, St John's wort and ginseng. These remedies are widely available and accessible without prescription in many countries. Therefore, co-treatment with antiretroviral therapy may occur, even without the knowledge of HIV clinicians (Peltzer et al, 2008).

Although herbal medicines are widely used there is inadequate evidence to support their use for HIV treatment. A Cochrane review of eight placebo-controlled randomized trials and one open-label study found insufficient evidence to conclude that the herbal medicines studied provided any beneficial effect on HIV treatment outcomes (Liu et al, 2005). However, lack of efficacy for HIV and the absence of clinically important effects are not synonymous. Because herbal medicines are likely to be co-administered with established HIV treatments (antiretroviral therapy), it is important to evaluate the potential risks and benefits of co-treatment.

Herbal medicines contain vast numbers of pharmacologically active compounds with potential for pharmacokinetic interactions with a wide range of pharmaceutical products (Fugh-Berman, 2000). Pharmacokinetic interactions which reduce antiretroviral drug exposure may increase the risk of selection of resistant strains of HIV and result in therapeutic failure. In contrast, interactions which improve antiretroviral exposure may have therapeutic benefit. However, concentrations of antiretroviral drugs which exceed the therapeutic range may increase the risk of toxicity and undermine patient adherence (Ladenheim et al, 2008). Importantly, drug–herbal interactions may be bi-directional and antiretroviral drugs may modify concentrations or efficacy of phytochemicals in herbal medicines.

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Antiretroviral drugs

HIV is a single-stranded positive-sense ribonucleic acid (RNA) virus which is characterized by a unique replication pattern involving transcription of deoxyribonucleic acid (DNA) from viral RNA. The replication steps involve viral entry into human cells, reverse transcription of viral RNA, integration of proviral DNA, transcription, translation, viral assembly and release. Antiretroviral therapy inhibits HIV replication by interfering with these steps. But antiretroviral therapy is not curative and lifelong, daily suppressive treatment is standard of care (Joint United Nations Programme on HIV/AIDS and World Health Organization, 2009).

Nevertheless, antiretroviral drug development represents one of the most significant medical achievements for a single disease. Since 1987, 25 agents have been approved for clinical use by the United States Food and Drug Administration. The approved classes of drugs include nucleotide reverse transcriptase inhibitors, non-nucleotide reverse transcriptase inhibitors, protease inhibitors, entry inhibitors and integrase inhibitors, while maturation inhibitors are at advanced stages of clinical development. In clinical practice, drugs from at least two different classes are used in combination for treatment of HIV. For example, in first-line therapy, most recommended regimens comprise two nucleotide reverse transcriptase inhibitors plus an non-nucleotide reverse transcriptase inhibitor or a protease inhibitor. With each patient receiving several antiretroviral drugs simultaneously, it is important to assess the potential for interactions for individual drugs within the antiretroviral therapy regimen.

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Potential for interactions with antiretroviral drugs

Apart from enfuvirtide, all currently approved antiretroviral drugs are orally administered. Drug interactions may occur during the processes of absorption from the gastrointestinal tract, drug distribution, drug metabolism and elimination. However, the potential for interactions varies depending on the class of antiretroviral drugs. The nucleotide reverse transcriptase inhibitors are pro-drugs which undergo intracellular phosphorylation during conversion to their active forms. For these drugs, intracellular concentrations appear to be more important than plasma concentrations in determining efficacy. Efficacy of raltegravir (an integrase inhibitor) also appears to be dependent on intracellular binding to the HIV pre-integration complex rather than plasma drug levels. Consequently, pharmacokinetic interactions involving drug concentrations in plasma may have only a minor impact on the efficacy of nucleotide reverse transcriptase inhibitors and integrase inhibitors.

Conversely, the protease inhibitors and non-nucleotide reverse transcriptase inhibitors have greater potential for drug interactions. These drugs are substrates, inducers or inhibitors for major drug transporters and drug metabolizing enzymes in the body. Other compounds which induce or inhibit these pathways can alter elimination of protease inhibitors and non-nucleotide reverse transcriptase inhibitors. Inhibition may involve competition between an inhibitor and the protease inhibitor or non-nucleotide reverse transcriptase inhibitor for the active site of the transporter or enzyme. Such interactions tend to occur rapidly and may have clinically important consequences. In contrast, induction is a gradual process involving protein synthesis of metabolic enzymes or transporters following prolonged exposure to an inducer. Generally, the maximal effect of induction is observed after several weeks. Key pathways influencing antiretroviral elimination are discussed below.

Cytochrome P450 metabolism

The cytochrome P450 (CYP) enzymes are a group of haem thiolate proteins which are responsible for metabolism of a wide variety of drugs. These enzymes are located on the smooth endoplasmic reticulum of hepatocytes and, less commonly, in the intestinal, brain, kidney and lung cells (Venkatakrishnan et al, 2001). The major isoform responsible for metabolism of protease inhibitors is CYP3A4 while non-nucleotide reverse transcriptase inhibitors are metabolized by CYP3A4 and CYP2B6. These enzymes are responsible for phase I metabolism of xenobiotics, a process which involves the generation of metabolites which are usually less potent than the parent compound. Clinically significant drug interactions involving protease inhibitors and non-nucleotide reverse transcriptase inhibitors are commonly mediated by induction or inhibition of CYP3A4 and CYP2B6. Induction leads to lower drug concentrations in plasma as a result of increased drug metabolism while inhibition may result in increased antiretroviral drug concentrations. Interestingly, one of the most potent inhibitors of CYP3A4 is a protease inhibitor known as ritonavir. Therapeutic doses of ritonavir have an unfavourable adverse event profile and are rarely used in clinical practice, but sub-therapeutic doses of ritonavir are routinely used to improve the bioavailability of co-administered protease inhibitors (boosting) by ritonavir's inhibition of CYP3A4.

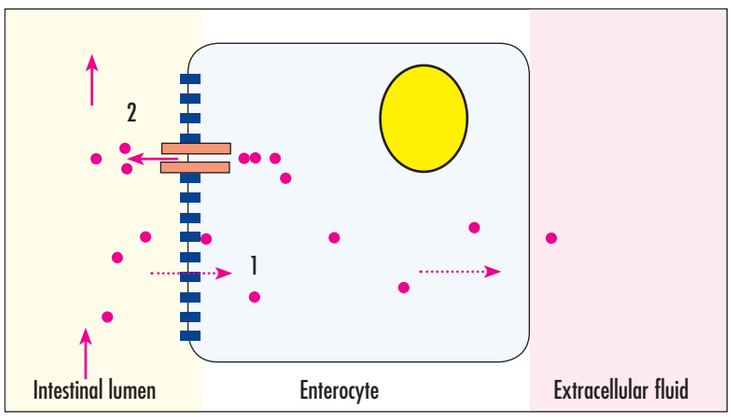
Other mechanisms

While CYP-mediated metabolism plays the major role in protease inhibitor and non-nucleotide reverse transcriptase inhibitor elimination, other pathways involved in the absorption and elimination of these agents also contribute.

P-glycoprotein is a 170 kDa transmembrane protein expressed in cells of the intestine, kidney and blood–brain barrier. On the luminal surface of enterocytes, P-glycoprotein acts as an efflux pump, expelling absorbed drugs back to the gastrointestinal lumen (*Figure 1*) and consequently reducing drug bioavailability. P-glycoprotein is a transporter of a wide variety of compounds including protease inhibitors (Owen et al, 2005). For the non-nucleotide reverse transcriptase inhibitors, efavirenz does not appear to be a substrate of P-glycoprotein (Janneh et al, 2009) but nevirapine studies showed conflicting results (Brown et al, 2008; Janneh et al, 2009). Inducers of P-glycoprotein increase its expression in enterocytes, limit gastrointestinal drug absorption and reduce antiretroviral drug levels in blood. In contrast, P-glycoprotein inhibitors will enhance drug absorption and consequently increase antiretroviral exposure.

Drug elimination is facilitated by the conversion of non-polar drug and metabolites to more soluble compounds (phase II metabolism). Glucuronidation is the most important pathway for phase II metabolism. Two

Figure 1. P-glycoprotein activity in the gastrointestinal tract. Note: (1) passive absorption of antiretroviral drugs from the gastrointestinal lumen and (2) active transport of absorbed drug by P-glycoprotein back to the gastrointestinal lumen.



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nucleotide reverse transcriptase inhibitors (zidovudine and abacavir) as well as metabolites of nevirapine and efavirenz undergo biotransformation involving glucuronidation (Belanger et al, 2009). In-vitro work suggests that protease inhibitors (notably atazanavir and indinavir) are inhibitors of the several uridine glucuronyltransferases (UGT1A1, UGT1A2 and UGT1A4). One of these transferases (UGT1A1) is also responsible for conjugation and subsequent elimination of endogenous bilirubin and interactions involving UGT1A1 inhibition may alter normal bilirubin metabolism (Zhang et al, 2005).

Herbal–antiretroviral interactions

Overall, research on antiretroviral interactions with herbal medicines has been constrained by methodological challenges. Few pharmacokinetic studies are available investigating pharmacokinetic interactions between herbal medicines and antiretroviral therapy and most of these studies were conducted in healthy volunteers and not among HIV patients who may have morbidities that alter drug absorption and metabolism. Instead, many data are derived from in-vitro studies characterizing the effect of herbal medicines on P-glycoprotein and CYP. However, in-vitro studies generally provide limited mechanistic information which may underestimate the contributions from other pathways for drug transport, metabolism and elimination.

In addition, standardization of herbal medicine preparations and dosages is problematic which may diminish the reproducibility of individual studies (MacDonald et al, 2009). Hence, herbal–drug interaction advice is often based on expert opinion supported by low quality evidence. In spite of these limitations, several clinically important interactions have been identified. Information on potential and known antiretroviral interactions with herbal medicines is available on websites such as www.hiv-druginteractions.org (*Figure 2*), but as information in the field changes rapidly, a formal check with an HIV pharmacist should be performed in each case in order to ensure that the most up-to-date information is considered during patient management.

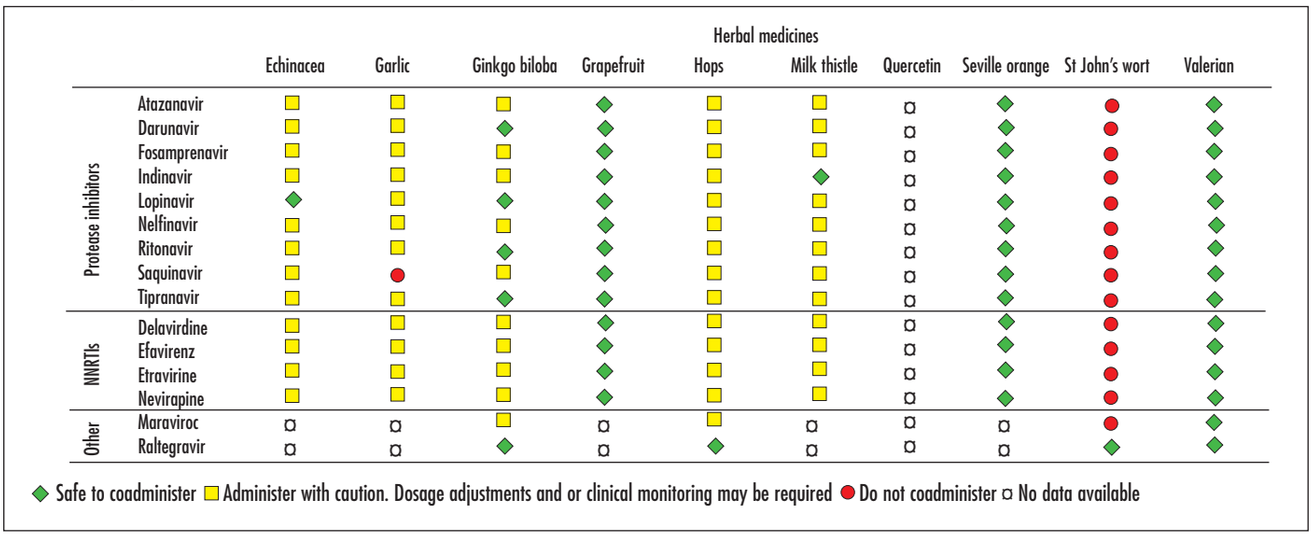
St John's wort

St John's wort (*Hypericum perforatum*) is one of the most commonly used herbal medicines in western countries. It contains several pharmacologically active phytochemicals including hyperforin, biflavonoids, tannins, xanthones, phloroglucinols and napthodianthrones. Patients with HIV may use St John's wort for treating mood disorders like depression. Although the precise mechanism of its antidepressive effect is unclear, it is postulated that its hyperforin inteferes with neurotransmitter uptake (Henderson et al, 2002). In a pharmacokinetic study in eight patients, St John's wort reduced indinavir's area under the curve by 54% (Piscitelli et al, 2000), possibly by induction of CYP3A4. The magnitude of this interaction raised concerns that concomitant use of St John's wort and protease inhibitors could result in treatment failure. Similarly, St John's wort was found to increase nevirapine clearance by 35%, resulting in low nevirapine plasma concentrations (de Maat et al, 2001). Consequently, St John's wort is contraindicated in patients receiving non-nucleotide reverse transcriptase inhibitors and protease inhibitors.

Garlic

Garlic (*Allium sativum*) is reported to have antimicrobial properties and beneficial effects on the cardiovascular system. In-vitro work demonstrated that garlic is an

Figure 2. Potential for interactions between antiretroviral drugs and herbal medicines. Adapted from the University of Liverpool antiretroviral drug interactions website (www.hiv-druginteractions.org). Readers should refer to the website for further information on a particular interaction. NNRTIs = non-nucleoside reverse transcriptase inhibitors.



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inhibitor of several CYP isoforms including CYP3A4 (Foster et al, 2001). However, this finding was contradicted by a subsequent healthy volunteer study using saquinavir as the sole protease inhibitor.

Saquinavir exposure was markedly diminished (51% reduction in saquinavir area under the curve) after repeated dosing with garlic supplements (Piscitelli et al, 2002). The reduction in saquinavir exposure is probably explained by CYP3A4 induction following prolonged exposure to garlic rather than inhibition. Thus, garlic is contraindicated in patients using non-boosted saquinavir.

Echinacea

Echinacea is traditionally used to improve immune function and prevent viral infections such as the common cold. It is an inducer of CYP3A4 and therefore expected to lower concentrations of drugs metabolized by this enzyme. However, echinacea did not significantly alter the pharmacokinetics of lopinavir when coadministered with ritonavir (Penzak et al, 2010). The authors suggest that the marked inhibitory effect of ritonavir may have overcome the inductive effects of echinacea on CYP3A4. Until additional data are available for other boosted protease inhibitors, it is prudent to monitor patients' antiretroviral therapy closely. Echinacea is a weak inhibitor of UGT1A1 and it is not expected to have clinically significant consequences on metabolism of substrates of UGT1A1 (Mohamed and Frye, 2011).

Milk thistle

Purportedly, milk thistle has beneficial effects on the liver and it is traditionally used to manage diseases like hepatitis and liver cirrhosis. In healthy volunteers, indinavir's pharmacokinetic parameters were not significantly reduced following 4 weeks of milk thistle administration. However, laboratory studies demonstrated that milk thistle has potential to inhibit CYP (MacDonald et al, 2009) and glucuronyltransferases including UGT1A1 and UGT2B7 (Mohamed and Frye, 2011). Hence caution is advised when using milk thistle with non-nucleotide reverse transcriptase inhibitors or protease inhibitors.

African herbal medicines

Herbal medicines in Africa are numerous and greatly varied reflecting marked geographical and cultural diversity on the continent. These plants are commonly used to meet primary health-care needs in regions with limited formal health services. In an ethnobotanical survey, investigators identified 103 medicinal plants used for treatment of HIV-related ailments and opportunistic infections in Uganda alone (Lamorde et al, 2010). Although, African herbal medicines are numerous, little is known about the potential for interactions for the vast majority of plants. This knowledge gap complicates efforts to integrate herbal medicines into national health systems already stretched by the HIV pandemic. In-vitro data from two popular South African plants (*Hypoxis hemerocallidea* and *Sutherlandia*) demonstrates that interactions are indeed possible. *H. hemerocallidea* and *Sutherlandia* were not only shown to inhibit CYP3A4 and P-glycoprotein in a microsome-based assay, but also to activate the nuclear receptor responsible for CYP3A4 and P-glycoprotein induction (Mills et al, 2005). Consequently, the use of these herbs should be avoided with protease inhibitors or non-nucleotide reverse transcriptase inhibitors.

Clinical approach to herbal interactions

The management of herbal antiretroviral interactions is challenging because of the large number of pharmacologically distinct herbal medicines which are being used in the context of steadily increasing number of antiretroviral drugs. Patients may not spontaneously disclose herbal medicine use so clinicians should adopt a direct questioning approach to obtain this history (Langlois-Klassen et al, 2008; Liu et al, 2009). Once a history of concurrent herbal use is obtained, support should be enlisted from HIV pharmacists and regularly updated drug interaction websites. Patient management may involve stopping the herbal medicine outright or close monitoring of antiretroviral therapy to ensure continued efficacy (Ladenheim et al, 2008). In some cases antiretroviral therapeutic drug monitoring may be warranted. Clinicians must be aware that herbal medicine use may be driven to a greater degree by cultural values and patient philosophy than by scientific evidence. Therefore clinical consultations should be conducted with a view to providing complete and up-to-date information about herbal interactions to enable patients to make appropriate choices for their own health. BJHM

Conflict of interest: none.

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KEY POINTS

- Herbal medicines are popular and co-treatment with antiretroviral therapy is common.
- Drug disposition of protease inhibitors and non-nucleoside reverse transcriptase inhibitors is influenced by cytochrome P450 and P-glycoprotein resulting in a significant potential for herbal–antiretroviral interactions.
- Clinicians should actively inquire about use of herbal medicines among HIV patients.
- When herbal medicine use is identified, a HIV pharmacist should be consulted to conduct a formal check for herbal–antiretroviral interactions.
- Herbal–antiretroviral interactions do occur but are often manageable if correctly identified.

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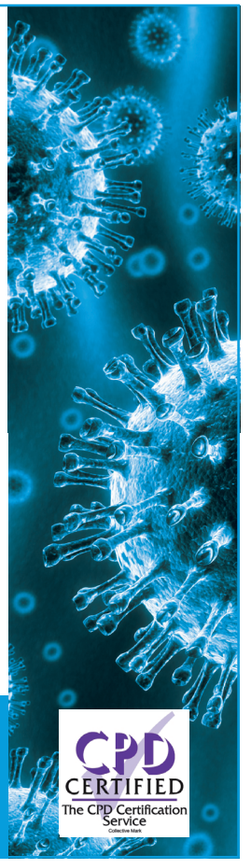

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