Interactions between Natural Health Products and Antiretroviral Drugs: Pharmacokinetic and Pharmacodynamic Effects

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Concurrent use of natural health products (NHPs) with antiretroviral drugs (ARVs) is widespread among human immunodeficiency virus–infected patients. This article reviews the clinical pharmacokinetic and pharmacodynamic interactions between NHPs and ARVs. Many NHPs are complex mixtures and are likely to contain organic compounds that may induce and/or inhibit drug metabolizing enzymes and drug transporters. Although the weight of evidence for the effects of certain NHPs varies and many studies of these products lack scientific rigor, it has been observed that St. John’s wort clearly induces cytochrome P450 3A4 and P-glycoprotein and reduces protease inhibitor and nonnucleoside reverse-transcriptase inhibitor concentrations, thereby increasing the likelihood of therapeutic failure. Limited clinical research suggests that intake of garlic and vitamin C results in reductions in ARV concentrations. The intake of milk thistle, Echinacea species, and goldenseal inhibits cytochrome P450 enzymes in vitro and may increase ARV concentrations, but by clinically unimportant amounts. Intake of fish oil reduces ARV-induced hypertriglyceridemia without significantly affecting lopinavir concentrations. Before recommending the use of NHPs as adjuncts to ARV use, studies should first exclude significant pharmacokinetic interactions and ensure that ARV efficacy is maintained.

The use of complementary and alternative medicine (CAM) is widespread; 35% of the population of the United States has reported the use of CAM. The most common and fastest growing CAM modality is herbal medicine. In 2002, 18.6% of adults in the United States reported using herbal medicines, which was an increase from 12.1% of adults in 1997 [1]. The use of CAM is even higher among HIV-infected patients [2]; CAM use has not decreased, despite the availability of effective antiretroviral (ARV) therapy. Surveys have revealed that 67% of HIV-infected patients receiving ARV therapy were also taking a natural health product (NHP) [3], of which the most common were vitamin C (63%), multivitamins (54%), vitamin E (53%), and garlic (53%); vitamin B12, beta-carotene, acidophilus, vitamin B6, zinc, ginseng, selenium, Echinacea species, vitamin A, aloe, folate, Chinese herbs, marijuana, goldenseal, and coenzyme Q10 were each reportedly taken by 20%–50% of patients [4]. CAM use is more likely in female subjects, white persons, individuals with lower depression scores [3], and individuals with higher incomes [5]. The major reasons reported by HIV-infected patients for using CAM modalities are a perceived additional efficacy, an increase in quality of life, a reduction of adverse effects of ARV therapy, and a feeling of control [5].

Physicians are often unaware of their patient’s use of CAM, as shown by a recent survey of HIV-infected subjects [6]. Physicians often have positive attitudes about CAM therapies; a survey in Massachusetts found that 63% of physicians believed that CAM was “often” or “usually” helpful for HIV-infected patients. More than one-third of physicians recommended CAM modalities, including 11% who recommended the intake of high-dose vitamins and 8% who recommended the use of herbal products [7]. It is commonly but mistakenly perceived by both health care providers and patients that NHPs are unlikely to be harmful, despite limited knowledge about their pharmacology and drug interaction potential. Thus, the number of HIV-infected patients taking NHPs concurrently with ARV therapy is unlikely to decrease and will become an increasingly important issue in patient management with the pro-
liferation of newer NHPs in the market. It is, therefore, critical to understand both the deleterious and beneficial pharmacokinetic interactions between NHPs and ARV drugs.

**CLINICAL SIGNIFICANCE OF PHARMACOKINETIC INTERACTIONS BETWEEN NHPS AND ARV DRUGS**

Protease inhibitors (PIs) and nonnucleoside reverse-transcriptase inhibitors (NNRTIs) have a relatively narrow therapeutic range, and antiviral activity closely correlates with their plasma concentrations [8, 9]. Subtherapeutic plasma concentrations of PIs [10] and NNRTIs [11], especially in proportion to the inhibitory concentration for the virus (IC₅₀), are associated with treatment failure and the emergence of viral resistance [12]. Conversely, elevated ARV concentrations may be associated with increased toxicity of some PIs [13] and NNRTIs [14].

NHPs are often complex mixtures of organic compounds, many of which can induce and/or inhibit the enzymatic pathways involved in the metabolism of ARV agents. Statistically, NHPs may be more likely than prescription drugs to inhibit and/or induce these pathways. Inducing the metabolic enzymes that clear ARVs may decrease the concentrations of these drugs, thereby decreasing their efficacy and possibly leading to treatment failure. These induction effects are more critical in treatment-experienced patients and in patients who may already have low ARV drug plasma concentrations because of poor adherence to therapy, malabsorption, or inadequate dosing. Conversely, inhibiting these metabolic enzymes can increase ARV drug concentrations and exacerbate their toxicity.

**MECHANISMS OF PHARMACOKINETIC INTERACTIONS**

**Cytochrome P450 3A4.** Most PIs and NNRTIs are mainly cleared by the intestinal and hepatic cytochrome P450 enzyme isofrom 3A4 (CYP3A4). NHP components can induce CYP3A4 activity. CYP3A4 induction is mediated through activation of a family of gene promoter systems known as xenobiotic response element systems. An important example includes the orphan nuclear receptor, pregnane X receptor (PXR), a transcription factor that is activated by structurally diverse foreign chemicals. The PXR regulates the transcription of a large set of genes that contribute to foreign compound metabolism and elimination, including the cytochrome P450s, drug transporters, and phase 2 enzymes [15]. PXR acts a heterodimer with the retinoid X receptor. The xenobiotic response element systems were designed to eliminate organic toxins in nature; thus, NHPs have great potential to activate this system, thereby increasing CYP3A4 activity and reducing ARV drug concentrations [16].

The best-studied NHP that increases CYP3A4 activity is St John’s wort (SJW). Some constituents of SJW, such as hyperforin, potently activate PXR in vitro [17]. Other NHPs have also been shown to contain substances that induce metabolism via xenobiotic response elements. Vitamin C can induce drug metabolism in animals [18]. Vitamin E induces PXR and CYP3A4 in vitro [19] and may reduce ARV drug concentrations.

Various plant substances may also inhibit the CYP3A4 iso-enzyme in vitro. The most commonly implicated classes of chemicals are flavonoids and polyphenols [20]. For example, the flavonoids naringenin and furanocoumarin bergamottin, each of which are components of grapefruit juice, are inhibitors of intestinal CYP3A4. Clinical studies of grapefruit juice in combination with PI therapy show an increase in systemic saquinavir concentrations but not in indinavir or amprenavir concentrations, possibly reflecting the differing importance of intestinal drug metabolism for these 2 agents [21–24]. Silybins, the active components of milk thistle, were found to inhibit CYP3A4 in vitro [25] and, thus, could increase ARV drug concentrations.

Some NHPs contain compounds that induce and inhibit enzymes at the same time. Garlic extracts are reported to inhibit CYP3A4 [26], but individual garlic constituents may also increase CYP3A4 expression [27]. Two herbs commonly used in Africa, African potato (Hypoxis hemerocallidea) and Sutherlandia frutescens, inhibited CYP3A4 but also induced PXR [28]. In the case of ginseng, the ginsenoside Rd weakly inhibits CYP3A4, but ginsenoside Rf increases its activity [29].

Plant constituents, such as polyphenols, are usually glycosylated and are inactive as enzyme inhibitors or inducers. These constituents can be activated by deconjugation mediated by intestinal enzymes or colonic microflora, which may explain some of the discrepancy between in vitro and in vivo findings. These active compounds may also undergo first-pass metabolism in the intestine [30]. Thus, in vitro experiments with herbal extracts may not predict in vivo effects.

**Drug transporter effects.** P-glycoprotein (P-gp) is a ubiquitous efflux drug transporter that affects a number of ARV drugs. Intestinal P-gp decreases oral bioavailability and plasma concentrations of some drugs in synergy with CYPs in the intestinal tract [31]. P-gp also reduces the penetration of PIs into sanctuary sites, such as the CNS; inhibition of P-gp enhances the distribution of substrate drugs into these sites [32]. P-gp reduces intracellular concentrations of some ARV agents and may be associated with a reduction in antiviral activity and with the development of resistance [33]. Thus, inhibition of P-gp may lead to increased antiviral effectiveness but increased toxicity, whereas P-gp induction can lead to therapeutic failure. On the other hand, P-gp induction inhibits cellular HIV production, which may counteract the effect of decreased ARV drug concentrations [34]. P-gp induction is also under the control of the PXR promoter system [35].
Silymarin, a component of milk thistle, inhibits P-gp activity and enhances doxorubicin toxicity in vitro [36]. Other NHPs that inhibit P-gp in vitro include garlic, green tea, turmeric, ginseng, rosemary, flavonoids from many plants [37], African potato, and S. frutescens [28]. However, data are lacking on the clinical significance of these effects on P-gp.

**Phase 2 enzymes.** The phase 2 enzymes include the glucuronosyl transferases and are responsible for conjugation reactions; these are the primary metabolic enzymes for zidovudine and abacavir. These enzymes are induced principally by activation of the antioxidant response element enhancer/promoter systems [35]. Many NHPs are antioxidants and may, therefore, induce phase 2 enzymes. For example, the glucosinolate sulfuraphane, which is found in cruciferous vegetables, such as broccoli [38] and the sulphur compounds found in garlic [39] are particularly potent phase 2 enzyme inducers and are mechanisms for these foods’ purported anti-aging and cancer-prevention properties [38]. The clinical significance of phase 2 enzyme induction by NHPs remains unclear.

**EXAMPLES OF CLINICAL PHARMACOKINETIC INTERACTIONS BETWEEN NHPS AND ARV DRUGS**

**Milk thistle.** Milk thistle (*Silybum marianum*) is commonly taken by patients who are coinfected with HIV and hepatitis virus, because it is purported to promote liver health [40]. Two uncontrolled clinical studies [41, 42] revealed trends toward reduction in concentrations of indinavir after coadministration of milk thistle. A 3-period, randomized, controlled trial revealed a similar trend; however, there was an even greater reduction in area under the curve (AUC; 21.5%), trough concentrations (Cmin; 53.1%), and peak concentrations (Cmax; 9.4%) in subjects in the control group, which persisted after a washout period [43]. Compared with the control group, the milk thistle group demonstrated a significant but small increase in Cmin and trends toward increases in AUC and Cmax (table 1). Other clinical studies involving milk thistle and CYP3A4 [44] or P-gp [45] probe drugs revealed no pharmacokinetic interactions, indicating that clinically important interactions between milk thistle and PIs or NNRTIs are unlikely.

**SJW.** SJW (*Hypericum perforatum*) is commonly used for depression, although current evidence of its efficacy for this condition is inconsistent [46]. Because depression is commonly observed in HIV-infected patients, there is a significant potential for the combined use of SJW and ARV drugs and, therefore, for interactions between these drugs. SJW is implicated in a multitude of clinically significant pharmacokinetic drug interactions with CYP3A4 and P-gp substrates [47]. Two clinical drug interaction studies—a single-sequence drug interaction study with indinavir [48] and a population pharmacokinetics study with nevirapine [49]—revealed reductions in ARV drug concentrations after SJW coadministration (table 1). The World Health Organization’s Collaborating Center for International Drug Monitoring has reported 1 case of reduction of drug activity in an indinavir-lamivudine-stavudine regimen coadministered with SJW that was associated with an increase in HIV plasma RNA [47].

Clinical evidence confirms SJW as a CYP3A4 inducer capable of decreasing concentrations of NNRTIs and PIs. SJW is, therefore, contraindicated in patients taking ARV drugs that are metabolized by the CYP3A4 pathway. Hyperforin may be the most active inducer of CYP3A4 found in SJW; the use of a low hyperforin preparation of SJW may reduce the risk of ARV drug interactions [50]. However, because the antidepressant activity of SJW has been linked to its hyperforin content [51], a low hyperforin preparation may be less efficacious; as well, other SJW components may be involved in CYP3A4 induction. Given the availability of alternative, effective antidepressants and the potential for deleterious drug interactions, one should avoid coadministration of SJW and ARVs.

**Garlic.** Garlic (*Allium sativum*) extracts are very commonly used by HIV-infected patients and are alleged to have anti-hyperlipidemic, antioxidant, and antimicrobial activities [52]. A clinical study of the saquinavir soft-gel formulation Fortovase (Roche Pharmaceuticals) found that coadministration of garlic significantly decreased saquinavir concentrations (table 1). Of note, a reduction in these concentrations occurred in only 6 of the 9 subjects studied. Because there were similar reductions in the magnitude of all concentration parameters, it is likely that garlic decreased saquinavir bioavailability, perhaps secondary to induction of intestinal CYP3A4 and/or P-gp. These parameters remained 30%–40% below baseline after a 10-day washout period [53], suggesting that there may be a long-lived systemic metabolite of garlic or a production of saquinavir metabolites that autoinduce metabolism. Unfortunately, this study lacked a control group, and the reduction in saquinavir concentrations in the washout period could be the result of a time-dependent autoinduction effect rather than a drug interaction. Saquinavir induces P-gp expression in vitro [54] and could reduce its own concentrations over time.

A 4-day study with ritonavir showed a nonsignificant trend towards reduction in AUC but not in Cmax with garlic [55]. One study showed that garlic oil did not have a significant effect on the pharmacokinetics of midazolam, a CYP3A4/5 substrate [56]. Another study involving healthy volunteers found that a different preparation of garlic also did not affect the pharmacokinetics of alprazolam, another CYP3A4 substrate [57]. Differences may be attributable to variations in garlic constituents [58], but it is not clear how these constituents can be measured or standardized [59].

One case report described 2 HIV-infected patients who were taking garlic supplements and who developed severe gastro-
Table 1. Clinical studies of the interaction between natural health products (NHPs) and antiretroviral (ARV) drugs.

<table>
<thead>
<tr>
<th>NHP, study</th>
<th>Year</th>
<th>Preparation; active ingredient content</th>
<th>Dosage</th>
<th>ARV drug, dosage</th>
<th>No. of subjects analyzed</th>
<th>Results</th>
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<tbody>
<tr>
<td>Milk thistle</td>
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<tr>
<td>Piscitelli et al. [42]</td>
<td>2002</td>
<td>Nature’s Way Thisilyn; 153 mg silymarins per tablet</td>
<td>One tablet 3 times per day for 3 weeks</td>
<td>Indinavir, 800 mg 3 times per day</td>
<td>10 (6 male subjects)</td>
<td>AUC(<em>{0-8}) decrease of 8% (90% CI, −28% to 2%); C(</em>{max}) decrease of 9% (90% CI, −22% to 6%); C(_{min}) decrease of 25% (90% CI, −37% to −10%); (P = .008)</td>
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<tr>
<td>DiCenzo et al. [41]</td>
<td>2003</td>
<td>General Nutrition Center; 173 mg silymarins per capsule</td>
<td>One capsule 3 times per day for 2 weeks</td>
<td>Indinavir, 800 mg 3 times per day</td>
<td>10 (7 male subjects)</td>
<td>AUC(<em>{0-8}) decrease of 7% (90% CI, −28% to 20%); C(</em>{max}) decrease of 11% (90% CI, −28% to 10%)</td>
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<tr>
<td>Mills et al. [43]</td>
<td>2005</td>
<td>Kare and Hope; 456 mg silymarins per capsule</td>
<td>One capsule 3 times per day for 4 weeks</td>
<td>Indinavir, 800 mg 3 times per day</td>
<td>16 (16 male subjects), 8 each in herb and control groups</td>
<td>AUC(<em>{0-8}), increase of 21% (90% CI, 14% to 72%); C(</em>{max}), increase of 5% (90% CI, 25% to 46%); C(_{min}), increase of 108% (90% CI, 16%−273%); (P = .047)</td>
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<tr>
<td>St. John’s wort</td>
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<tr>
<td>Piscetelli et al. [48]</td>
<td>2000</td>
<td>Hypericum Buyer’s Club; 300 mg tablet containing 0.3% hypericin</td>
<td>One tablet 3 times per day for 2 weeks</td>
<td>Indinavir, 800 mg 3 times per day</td>
<td>8 (6 male subjects)</td>
<td>AUC(<em>{0-8}), decrease of 57% (SD, 19%); (P = .0008); C(</em>{max}), decrease of 28%; C(_{min}), decrease of 90% (90% CI, 97% to 65%); (P = .027)</td>
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<tr>
<td>De Maat et al. [49]</td>
<td>2001</td>
<td>Various; not stated</td>
<td>Not stated</td>
<td>Nevirapine, usual treatment dose</td>
<td>5 HIV-positive case patients (5 male subjects), 176 HIV-positive control subjects; population pharmacokinetics</td>
<td>CL/F, increase of 35% (SD, ±15%); (P = .02)</td>
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<td>Garlic</td>
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<tr>
<td>Piscetelli et al. [53]</td>
<td>2002</td>
<td>Natrol GarliPure, maximum allicin formula; 11.2 mg allicin per capsule</td>
<td>One capsule 2 times per day for 3 weeks</td>
<td>Saquinavir-sgc (Fortovase), 1200 mg 3 times per day</td>
<td>9 (4 male subjects)</td>
<td>AUC(<em>{max}), decrease of 51% (90% CI, −69% to −21%); (P = .007); C(</em>{max}), decrease of 54% (90% CI, −73% to −24%); (P = .006); C(_{min}), decrease of 49% (90% CI, −65% to −26%); (P = .002)</td>
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<td>Gallicano et al. [55]</td>
<td>2003</td>
<td>Nature Source Odourless Garlic Life Brand; allicin not detected</td>
<td>Two 5-mg capsules, equal to 1 g fresh garlic, 2 times per day for 4 days</td>
<td>Ritonavir, 400 mg single doses</td>
<td>10 (5 male subjects)</td>
<td>AUC(<em>{max}), decrease of 17% (90% CI, −31% to 0%); C(</em>{max}), decrease of −1% (90% CI, −25% to 31%)</td>
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<td>Vitamin C</td>
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<tr>
<td>Slain et al. [61]</td>
<td>2005</td>
<td>Not stated</td>
<td>1000 mg per day for 1 week</td>
<td>Indinavir, 800 mg 3 times per day</td>
<td>7 (6 male subjects)</td>
<td>AUC(<em>{max}), decrease of 15% (90% CI, −25% to −5%); (P = .05); C(</em>{max}), decrease of 23% (90% CI, −35% to −12%); C(_{min}), decrease of 32%; (P = .09) (NS)</td>
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<td>Goldenseal</td>
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<tr>
<td>Sandhu et al. [64]</td>
<td>2003</td>
<td>Nature’s Way Goldenseal Root Herbal Single; 2.0% hydrastine, 2.96% berberine</td>
<td>Two 570-mg capsules, 2 times per day for 2 weeks</td>
<td>Indinavir, 800 mg single dose</td>
<td>10 (6 male subjects)</td>
<td>C(_{max}), increase of 7% (90% CI, −13% to 23%); CL/F, decrease of 7% (90% CI, −21% to 8%)</td>
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<tr>
<td>Fish oil</td>
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<tr>
<td>Gerber et al. [79]</td>
<td>2006</td>
<td>Advanced Nutritional Technology; 500 mg EPA, 310 mg DHA</td>
<td>Three 1-g capsules, 2 times per day for 8 weeks</td>
<td>Various ARV drugs, dose not stated</td>
<td>90 subjects total received fish oil, 18 received lopinavir/ritonavir</td>
<td>C(_{max}), decrease of 9%, NS</td>
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</table>

**NOTE.** All subjects are HIV-negative volunteers, unless otherwise indicated. AUC\(_{0-8}\), area under the curve from hour 0 to hour 8; AUC\(_{0-\infty}\), area under the curve from hour 0 to infinity; C\(_{max}\), peak concentration; C\(_{min}\), trough concentration; CL/F, apparent oral clearance; NS, no significant change.
intestinal toxicity after starting ritonavir therapy. Symptoms recurred after rechallenge with low-dose ritonavir, suggesting that elevated ritonavir concentrations were not the cause [60]. Ritonavir may have inhibited the metabolism of garlic, thereby leading to a pharmacokinetic interaction, or it may have potentiated the toxic effects of garlic on the intestinal tract, thereby leading to a pharmacodynamic interaction.

**Vitamins.** Vitamins are the most widely used NHP among HIV-infected patients [4]. Patients use a wide variety of vitamin doses and combinations, thereby making it extremely difficult to understand potential drug interactions. A single-sequence study showed significant reduction in the indinavir AUC for 0–8 h (but not in the AUC for 0–5 h) and Cmax after 1 week of ingestion of vitamin C at a dosage of 1000 mg daily [61]. Two of the 7 subjects showed no decrease in AUC for 0–8 h (but not in the AUC for 0–5 h) and Cmax after 1 week of ingestion of vitamin C at a dosage of 1000 mg daily [61].

**Goldenseal.** Goldenseal root (*Hydrastis canadensis*) is purported to have immunostimulatory properties [62]. In vitro studies have reported that goldenseal is a potent CYP3A4 inhibitor [63]. A clinical interaction study of 1140 mg of goldenseal root (administered twice daily for 2 weeks) and indinavir showed no change in indinavir pharmacokinetics [64] (table 1). Another clinical study showed that 900 mg of goldenseal extract administered 3 times per day for 4 weeks significantly decreased the ratio of midazolam metabolite to parent compound, thereby indicating inhibition of CYP3A4 activity [65]. Patients taking goldenseal should be monitored for increased toxicity of CYP3A4 substrate drugs with a low therapeutic ratio.

**Echinacea species.** *Echinacea* species products are commonly used for their purported immunostimulatory properties—for example, to prevent respiratory infections [62]. *Echinacea augustifolia* extracts inhibit CYP3A4 in vitro [63]. One clinical study found that an 8-day course of 400 mg of *Echinacea purpurea* root extract administered 4 times daily increased the systemic clearance of midazolam, a CYP3A4 substrate, by 33%. However, bioavailability of midazolam increased by the same amount, leading to no overall change in AUC [66]. This result demonstrated a complex interaction in which hepatic CYP3A4 is induced but intestinal CYP3A4 and/or P-gp is inhibited. A second study showed no effect of *E. purpurea* on the pharmacokinetics of oral midazolam [67]. Caution should be exercised, however, because *Echinacea* extracts, like many other herbal products, are not chemically standardized; extracts containing different constituents may produce different effects on ARV drug concentrations.

**Other herbs.** The following herbs have no observed effects on the concentrations of midazolam, a CYP3A4 probe, in clinical studies: kava kava (*Piper methysticum*), black cohosh (*Cimicifuga racemosa*), valerian (*Valeriana officinalis*) [65], Panax ginseng, Ginkgo biloba [56], bitter orange (*Citrus aurantium*), saw palmetto (*Serenoa repens*) [67], and Siberian ginseng (*Eleutherococcus senticosus*) [68]. These findings suggest that clinically significant pharmacokinetic interactions between these herbs and PIs or NNRTIs are unlikely.

**Practical considerations.** Most clinical pharmacokinetic interaction studies with NHPs lack control groups to account for time-dependent changes in drug concentrations, as was observed for indinavir in the milk thistle study by Mills et al. [43]. In addition, almost no pharmacokinetic interaction studies so far have been conducted with HIV-infected patients. The few pharmacokinetic studies that have been performed are outdated and have not kept pace with standard of care. For example, indinavir and saquinavir are now rarely used without ritonavir, and the impact of NHPs on these combinations is unknown. There are still no studies examining the PIs lopinavir, atazanavir, tipranavir, fosamprenavir, or darunavir, and the NNRTI efavirenz. Therefore, it is difficult to extrapolate these data to regimens that are commonly administered to HIV-infected patients today.

NHPs are loosely regulated by the US Food and Drug Administration, and there is great variability in recommended dosages and labeling [69]. There is no requirement to standardize NHPs to any chemical components, and, thus, there may be great variability in the content of active constituents, even among different brands of the same herb [70]. Different contents of inhibiting and inducing chemicals can contribute to contrary results in pharmacokinetic interaction studies. In some cases, commercial products may not contain the labeled herb at all [71], thereby confounding the interpretation of pharmacokinetic drug interaction studies. Results from one study are, therefore, not generalizable to other dosages, formulations, and brands of NHPs.

**EXAMPLES OF CLINICAL PHARMACODYNAMIC INTERACTIONS BETWEEN NHPS AND ARV DRUGS**

**ARV activity.** NHPs may have direct effects on HIV [72], thereby augmenting or antagonizing the therapeutic effects of ARV drugs. For example, SH, a combination of 5 Chinese herbs (*Glycyrrhiza glabra*, *Artemisia capillaries*, *Morus alba*, *Astragalus membranaceus*, and *Carthamus tinctorius*) was found to reduce HIV replication through nonprotease or reverse-transcriptase inhibitor mechanisms [73]. SH was compared with a placebo in a group of 82 HIV-infected Thai patients receiving a regimen of zidovudine and zalcitabine. There was a significant decrease in viral load (−1.4 log) and an increase of 98 cells/mm³ in CD4+ cell count at week 24 in the SH group, compared with the
placebo group [74]. However, the control, dual-ARV therapy regimen used in this trial is now considered to be suboptimal for the treatment of HIV infection and, therefore, the significance of these findings is unclear. According to a Cochrane systematic review [75], other published studies of herbs have shown no additive effect on ARV therapy to date.

Some studies have shown that NHPs may also indirectly enhance ARV therapy by boosting the immune system [76], whereas others have suggested that these agents may be immunosuppressive and, thus, could exacerbate HIV infection [77]. Clinical research data of good quality are lacking.

**ARV-associated toxicity.** NHPs have effects on metabolic pathways that are affected by ARV drugs and can thereby exacerbate or alleviate ARV drug–associated toxicity. PI treatment is associated with hyperlipidemia [78]; fish oil has been shown to alleviate ARV therapy–induced hypertriglyceridemia alone and in combination with fenofibrate. In 100 hypertriglyceridemic subjects receiving ARV therapy who were also taking fish oil (1g capsules containing 500 mg EPA [eicosapentaenoic acid] and 310 mg DHA [docosahexaenoic acid]; Advanced Nutritional Technology) at a dose of 3 capsules twice daily for 8 weeks, triglyceride concentrations decreased from >400 to <200 mg/dL in 8.5% of subjects; of those who did not respond to fish oil or fenofibrate alone, 22.7% responded to combination therapy. Fish oil alone decreased triglyceride levels by 46%. There was no significant effect of fish oil on CD4+ cell counts or immune function, and there was a nonsignificant 9% decrease in lopinavir trough concentrations, thereby demonstrating the safety of using fish oil together with PIs [79]. The US Food and Drug Administration recently approved Omacor, a different fish oil preparation, for treatment of hypertriglyceridemia; because this product is administered at a lower dose of 4 g per day, it is also unlikely to interact with PIs.

Another common adverse effect of PI therapy that may be improved by NHPs is diarrhea. A phase 2 study involving 51 patients with AIDS who had diarrhea revealed that 4 days of administration of SP-303, an extract of Croton lechleri, reduced stool weight (mean reduction of stool weight [from baseline] on day 4 of treatment, by 451g per 24 h for those receiving SP-303 vs. by 151g per 24 h for those receiving placebo; \( P = .14 \)) and frequency (mean reduction of frequency of stools [from baseline] on day 4 of treatment, by 3 per 24 h for those receiving SP-303 vs. by 2 per 24 h for those receiving placebo; \( P = .30 \)). By random regressions model of daily measurements (over 4 days), patients treated with SP-303 experienced a significant reduction in stool weight (\( P = .008 \)) and in stool frequency (\( P = .04 \)) [80].

**CONCLUSIONS**

NHP use is widespread among HIV-infected patients receiving ARV therapy, and it often occurs without the approval or even the knowledge of the treating physician. As a result, there is a great potential for pharmacokinetic and pharmacodynamic interactions between NHPs and ARV drugs. NHPs are not inert substances, and there are clear examples of clinically significant interactions with ARV agents that may be beneficial or harmful to patients.

There is often a lack of scientific rigor in studying these interactions. For the most part, NHPs are not well standardized. Data from published studies are often suboptimal, contradictory, and outdated, and new studies are urgently needed. NHPs should be studied in the same rigorous scientific fashion as conventional drugs whenever possible. In the meantime, caution should be exercised and clinicians should always be vigilant to the possibility of interactions between NHPs and ARV drugs in their patients.

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**References**


55. Markowitz JS, Devane CL, Chavin KD, Taylor RM, Ruan Y, Donovan JL. Effects of garlic (Allium sativum L.) supplementation on cytochrome


