Farm Hosp. 2009;**33(1)**:31-6

Farmacia HOSPITALARIA

www.elsevier.es/farmhosp

ORIGINAL ARTICLE

The influence of alternative medicine in highly active antiretroviral treatment

M. Vázquez Hernández,[a,*] M.F. Hurtado Gómez,[a] and J.R. Blanco[b]

[a]*Servicio de Farmacia Hospitalaria, Hospital San Pedro, Logroño, La Rioja, Spain*
[b]*Servicio de Enfermedades Infecciosas, Hospital San Pedro-CIBIR, Logroño, La Rioja, Spain*

Received May 19, 2008; accepted January 26, 2009

KEYWORDS
HAART;
Medicinal plants;
Drug interactions;
HIV

Abstract
Objective: Over the last few years, there has been a notable increase in the use of alternative medicine by the general population. The aim of this study is 2-fold. Firstly we will analyse the incidence of the use of medicinal plants in patients with HIV undergoing Highly Active Anti-Retroviral Therapy (HAART). Secondly, with the help of existing bibliographic information, we want to study the existence of possible interactions.
Material and method: We carried out a prospective study with a targeted interview (October to December 2007) on consenting patients with HIV undergoing HAART treatment.
Results: Of the 193 patients that agreed to take part in the survey, 16.6% confirmed they used alternative medicinal therapies. In 46%of the cases there was a potential interaction with the effectiveness of HAART. Forty-six percent of the potential interactions were in the case of the patients who used grapefruit as an alternative medicine, 21%in the case of patients using thistle and Echinacea respectively, 4%for those using omega-3, Chinese herbs, and ginseng.
Conclusion: There is a significant use of natural products by these groups of patients, of which a significant percentage interact with HAART. A better understanding of the possible interactions with HAART and improved information offered to patients with HIV is needed.

PALABRAS CLAVE
Tratamiento antirretroviral;
Plantas medicinales;
Interacciones medicamentosas;

Influencia de la medicina alternativa en el tratamiento antirretroviral de gran actividad

Resumen
Objetivo: En los últimos años hemos asistido a un aumento notable en el uso de la medicina alternativa por parte de la población actual. El objetivo de este trabajo es doble. Por un lado, se pretende analizar la incidencia del uso de plantas medicinales en pacientes infectados por el

*Corresponding author.
E-mail address: mvazquez@riojasalud.es (M. Vázquez Hernández).

Virus de la inmunodeficiencia humana

virus de la inmunodeficiencia humana (VIH) en tratamiento antirretroviral de gran actividad (TARGA). Por el otro, conocer la existencia de posibles interacciones con la ayuda de bases bibliográficas documentadas.

Material y métodos: Estudio prospectivo —entrevista dirigida—(octubre-diciembre de 2007) realizado en pacientes infectados por el VIH y en TARGA que aceptaron realizar la encuesta.

Resultados: De los 193 pacientes que accedieron a la entrevista, el 16,6%de los pacientes afirmaron usar tratamientos de medicina alternativa. De ellos, en el 46% de los casos había una interacción potencial con la eficacia del tratamiento antirretroviral. Éstas se dieron en un 46% con el pomelo, en un 21%en el caso del cardo y de la equinácea, respectivamente, y fue de un 4%tanto para omega-3 y hierbas chinas, como para ginseng.

Conclusión: Hay un consumo importante de productos naturales por parte de este grupo de pacientes, de los cuales un porcentaje significativo interaccionan con el TARGA. Se hace preciso tener un conocimiento mayor de las posibles interacciones en los pacientes con tratamiento antirretroviral y ofrecer más información a los pacientes infectados por el VIH.

Introduction

Human immunodeficiency virus (HIV) infection is caused by the HIV virus. Although the eradication of HIV is not currently possible, highly active antiretroviral treatments (HAART) prevents viral replication, re-establishes immunological function, reduces morbi-mortality, and improves the quality of life of the patient infected with HIV.[1]

There are several factors that can have a negative impact on achieving the desired effects. One of these is the interaction of HAART with phytotherapeutic substances. At present, there has been an increase in the use of medicinal plants (alternative medicine) in our environment. The use of medicinal plants has a high risk of interaction with HAART.[2] This risk is increased in drugs with a narrow therapeutic margin, since phytotherapeutic products are complex mixes of organic compounds, they can induce or inhibit the enzymes responsible for metabolism in HAART. As a result, the plasma concentrations of these drugs can be reduced and therefore their efficacy diminished, or, on the contrary, increased, which would exacerbate their toxicity.[3] The aim of this study is to analyse the incidence of the use of medicinal plants in patients infected with HIV and undergoing HAART, as well as analyse the existence of possible interactions with the help of the literature documented.

Material and methods

A prospective study was carried out (October-December 2007) in the outpatient clinic at the Hospital Pharmacy Department at Hospital San Pedro in Logroño. The patients had to infected with HIV, be receiving HAART and attending the hospital's Infectious Disease Department on a regular basis.

A bibliographical search was performed on PubMed for articles published on interactions between antiretroviral drugs and medicinal plants. A search was also performed on the web pages of scientific organisations with databases on interactions, which were considered relevant, between these 2 therapeutic groups.

The following medical terms, extracted from the MeSH database, were used: "herbal medicine," "herb," "phytoterapy," "interactions," "drug interactions and antiretroviral." In addition, the following databases were consulted:

a) www.interaccioneshiv.com (Spanish Society of Hospital Pharmacy).
b) www.hiv-druginteractions.org/frames.asp?drug/drg_main.asp (University of Liverpool).
c) www.cofbizkaia.net/COFBI/Publicaciones.nsf/fwContNumeros?OpenForm&rev = Argibideak (Basque Professional Association of Pharmacists).

Table 1 summarises the clinical repercussions of the interactions of medicinal plants on the efficacy and toxicity of antiretroviral treatment.

The patients who participated in the study had to complete a targeted questionnaire on the use of alternative medicine, where alternative medicine is understood as "the branch of medicine that compiles non-conventional medical systems, diagnostic methods and therapeutic approaches, both ancient and modern, to understand and validate them and in this way offer them to the public as alternatives or supplements to current conventional medicine," definition of the 2002 World Health Organization.[4] The interview included aspects such as whether they considered medicinal plants as drugs, whether those interviewed had notified their doctor of their use or whether they had never been specifically asked. The following questions were asked: Do you take medicinal plants, herbs, infusions, or any type of substance as an alternative to antiretroviral medication? In the event of a positive response: Which one(s)? Do you think that these substances could affect the efficacy of the antiretroviral treatment? In the event of a positive response: In what way? Why have these not been recorded in your pharmacotherapeutic history? The variables included in the study were taken from the SELENE[5] computer program, which collects patients' clinical history (age, sex, how the patient was infected with the HIV virus, the HIV plasma viral load, and CD4 lymphocytes amount). Adherence to HAART was analysed using the calculation in the PRISMA program for dispensing medication to external patients.[6]

Table1 Clinical repercussion of the interaction of medicinal plants on the efficacy and toxicity of antiretroviral treatment

Plant	Interaction mechanism	Antiretroviral	Effect	Type of interaction
Grapefruit[10,11]	Inhibits CYP3A4	PI NNRTI	Concentrations of indinavir reduce by between 15%and 30% Increases the concentration of saquinavir	Moderate interaction
Milk thistle[12]	Induces CYP3A4	PI NNRTI	Reduces concentrations of indinavir (ABC 21%)	Moderate interaction
Echinacea[3-9,13,14]	Inhibits CYP3A4 and intestinal P-glycoprotein, but induces hepatic CYP3A4	PI NNRTI NARTI	Reduction in plasma values. Values of saquinavir can increase (due to the effect on CyP3A4)	Association contraindicated
Omega-3[21-25]				Beneficial effects as reduces the risk of hypertriglyceridemia
Chinese herbs[21-25]				Beneficial effects
Ginseng[21-25]	Induces CYP3A4		Reduces plasma concentrations of antiretroviral drugs	Moderate interaction
Valerian[21-25]			Increases the hepatic toxicity with hepatotoxic drugs	Slight interaction
Marijuana[3-9,13,14]		Nelfinavir Indinavir	Reduces the Cmax of nelfinavir by 17%, and the Cmax of indinavir by 34%	Potential interaction that may require dose adjustment
Hypericum[3-9,13,14]	Pharmacokinetic interaction with CYP3A4 and P glycoprotein	PI	Reduced indinavir by 57% and nevirapin by 35%, probably other PIs also	Association contraindicated
Garlic[3-9,13,14]	Induces CYP3A4 and *P*glycoprotein	PI NNRTI	Reduces saquinavir by 50% The metabolism of ritonavir can be inhibited by garlic, with toxic effects	Moderate interaction
Cat's claw[21-25]	Inhibits CYP3A4	PI NNRTI	Increases the half-life and serum values	Moderate interaction

AUC indicates area under the curve; C_{max}, maximum concentration; NARTI, nucleoside analogue reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

The data were codified and entered into a database (Microsoft Access 2007). A spreadsheet (Microsoft Excel Office, 2003) and the SpSS® v12.0 statistical program were used for statistical processing. To find an association between 2 nominal qualitative variables, we used the χ^2 test and when we were working on an association between qualitative and another quantitative variable, we used the non-parametric Mann-Whitney *U* or Kruskal Wallis tests. There was statistically significant variance when *P* was lower than .05.

Results

A total of 193 (44.33%) patients initially participated in the study. Of these patients, the average age (standard deviation) was 43.8 (10.51) years, and 67.3% were male. Of the 193 patients, 32 (16.6%) confirmed that they did consume 1 or more medicinal plants. Table 2 shows their characteristics. Of the 32 patients who consumed some medicinal plant, in 12 (37.5%) there was bibliographic information warning of the toxic potential.

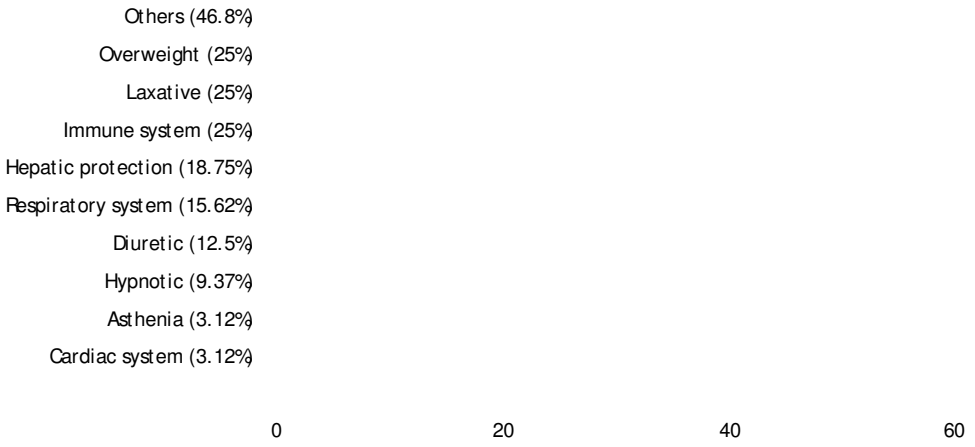

Figure 1 Alternative medicine consumed and distributed based on pharmacological activity. "Others" includes the following products: grapefruit, marijuana, aloe vera, Chinese herbs, Bermuda grass, angelica, soya, brewer's yeast, and cat's claw.

Table 2 Characteristics of the patients analysed

	Patients undergoing HAART (n=193)	Patients undergoing HAART who use alternative medicine (n=32)
Average age, y	43.89	44.93
Males, %	67.36	65.63
Contamination method, %		
PDU	63.21	65.63
Others	36.79	34.37
HIV stage, %	12.95	15.63
Viral load <50 copies/mL, %	74.61	81.25
CD4 lymphocytes, average	529.6	
Adherence, %	94.16	93.79

HAART indicates high activity antiretroviral treatment; PDU, parenteral drug user.

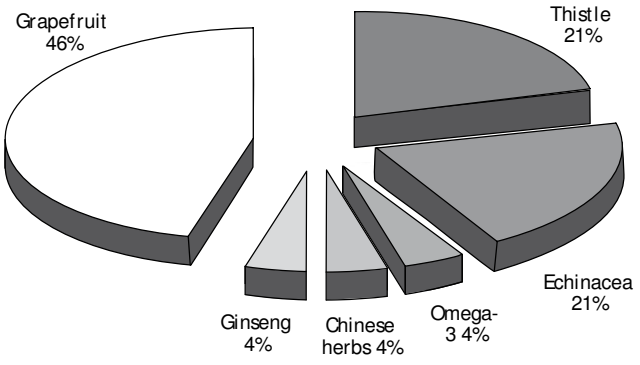

Figure 2 Medicinal plants most consumed by patients undergoing treatment with antiretroviral drugs.

Among the patients who took medicinal plants, 37.5% considered this medication. The same percentage (37.5%) did not know that medicinal plants could produce adverse effects and 100% did not know that these treatments could have a negative effect on their HAART. Among the patients undergoing HAART who consumed some type of medicinal plant, 21.9% were taking nucleoside analogue reverse transcriptase inhibitors, 34.4% protease inhibitors, and 43.7% non-nucleoside reverse transcriptase inhibitors. There are no statistical differences in any of the variables studied (age, sex, method of contamination, plasma viral load, CD4 lymphocytes amount, adherence, or HAART type) between the group of patients who consumed medicinal plants and the remaining patients.

Figure 1 describes the pharmacological properties of the products used. The results are shown in relation to the total number of patients who confirmed that they consumed some sort of herbal medicine and therefore the sum is greater than 100%. A total of 20 patients (62.5%) confirmed that they consumed just 1 medicinal plant; 9 (28.1%) confirmed that they consumed 2 medicinal plants; and 3 (9.4%) confirmed that they consumed 3 or more medicinal plants. Figure 2 shows the percentage of medicinal plants which are most consumed by patients in HAART treatment. Of the total medicinal plants that patients confirmed to consume, no bibliographical references were found for 54% of these in relation to possible adverse reactions with the antiretroviral medication taken. However, information on the influence on the efficacy of HAART was found in the literature for 46% of the medicinal plants consumed (11 cases of grapefruit, 5 cases of Echinacea, and 5 of milk thistle).

Discussion

Patients undergoing HAART regularly use medicinal plants and this often occurs without the knowledge of the doctor or pharmacist. There is evidence that herbal preparations can cause pharmacokinetic and pharmacodynamic interactions

that represent a potential risk in patients undergoing HAART.[3] Although we found examples of clinically non-significant interactions with antiretroviral agents, there are others that can have serious consequences on the treatment's efficacy.

Despite the fact that the actual prevalence of the consumption of medicinal plants in the Spanish population is not exactly known, it has without doubt increased significantly in recent years.[7] However, some results may help extrapolate these data. A total of 19.6% patients from primary care confirmed consumption; 34.7% from external digestive consultations have consumed some sort of medicinal plant; and 35.7% from anaesthetic consultations also confirmed consumption of some sort of medicinal plant.[8] In our study, the results are similar to those observed in primary care (19.6% above and 16.6% in this study).

The population in general and the patients perceive these substances as healthy. The patients are not aware of the adverse effects that these can sometimes produce and that they can even cause HAART to fail. The reasons given for the consumption of medicinal plants is that the patients believe that these increase the efficacy of their treatment, improve their quality of life, reduce the adverse effects of HAART and give them a feeling of control.[9]

As observed in this study, a significant percentage of our patients confirm that they are taking some type of medicinal plant, although we found very limited bibliographical information on the possible adverse interactions relating to some of these products.[10-14] However, other plants do cause interactions, such as grapefruit, milk thistle or Echinacea.[3,15-18]

Another interesting aspect is that, in our environment, 62.5% of patients who were taking medicinal plants did not know exactly what type they were taking, could not say what their specific effect was and many had starting using them simply following recommendations from non healthcare individuals. A total of 37.5% of patients taking medicinal plants did not know that these could have damaging health effects. Indeed, none of them informed their doctor or pharmacist in a normal consultation. These results coincide with other studies performed in our environment.[7] One of the reasons cited for not informing their doctors was the lack of awareness that medicinal plants are indeed medication.

Given these data, patients must be directly questioned on the consumption of these products and specifically informed both by the doctors and pharmacists.

There has been little research into the interactions between antiretrovirals and treatment with medicinal plants. However, in some cases there is ample scientific evidence upon which to base recommendations (for example, *hypericum*, garlic, Echinacea, marijuana).[3,18-25]

In order to reduce the risk of interactions, it would be useful to perform targeted questionnaires on the use of medicinal plants, both in the pharmacy and in the medical services. This must be performed by the healthcare professional to improve the efficacy of the antiretroviral treatment, since there are data indicating that patients require better communication to obtain more information on certain habits.

Finally, there is a significant scientific gap in the study of medicinal plants and HAART. In some cases, the studies published are scarce or even contradictory.[10-25] Knowledge on the potential interactions between many of these medicinal plants and the different HAARTs must be improved.

Conflict of interest

This article has not been previously published and there are no conflicts of interest.

References

1. Recomendaciones de Gesida/Plan Nacional sobre el Sida respecto al tratamiento antirretroviral en adultos infectados por el virus de la inmunodeficiencia humana (Updated January 2008) [Accessed April 28, 2008]. Panel de expertos de Gesida y Plan Nacional sobre el Sida. Available from: http://www.gesida.seimc.org/index.asp
2. Izzo AA. Herb-drug interactions: an overview of the clinical evidence. Fundamental Clinical Pharmacology. 2004;19:1-16.
3. Lee LS, Andrade AS, Flexner C. Interactions between Natural health products and antiretroviral drugs. Pharmacokinetic Pharmacodynamic Effects. 2006;43:1052-9.
4. ¿Qué es la Sociedad Peruana de Medicina Alternativa y Complementaria? (SPEMAC) [cited April 28, 2008]. Sociedad Peruana de Medicina Alternativa y Complementaria. Available from: http://www.geocities.com/spemac2000/Quienessomos.htm
5. Sánchez Ros N, Reigosa Gago LF. Selene. Informatización de la historia clínica electrónica: implicación sobre el proceso de enfermería. Enfermería Global [journal online] 2006; 8 [cited April 28, 2008]. Available from: http://www.um.es/eglobal
6. Planells C. Prescripción asistida por ordenador [monograph online] Ediciones Mayo; 2002 [cited April 28, 2008]. Available from: http://www.combino-pharm.es/upload/publicaciones/inscripcion.pdf
7. Valencia Orgaz O, Orts Castro A, Castells Armenter MV, Pérez-Cerdá Silvestre F. Valoración del consumo preoperatorio de plantas medicinales en la consulta preanestésica. Rev Esp Anestesiol Reanim. 2005;52:453-8.
8. Tres JC. Interacción entre fármacos y plantas medicinales. An Sist Sanit Navar. 2006;29:233-52.
9. Diggan J, Peterson WS, Schutz M, Khuder S, Charkraborty J. Use of complementary and alternative therapies in HIV-infected patients. AIDS Patient Care STDS. 2001;15:159-67.
10. Piscitelli SC, Burstein AH, Welden N, Gallicano KD, Falloon J. The effect of garlic supplements on the pharmacokinetics of saquinavir. Clin Infect Dis. 2002;34:234-8.
11. Muñoz MJ, Frías S, Sánchez VR, Castillo I. Interacciones entre plantas medicinales y fármacos. Actualidad terapéutica. Centro de Información del Medicamento del Colegio de Farmacéuticos de Madrid. 2002;2:1-16.
12. Zardain E. Plantas medicinales: interacciones adversas. FarmAs. 2003;12:1-6.
13. de Truchis P, Kirstetter M, Perier A, Meunier C, Zucman D, Force G, et al. Reduction in triglyceride level with N-3 polyunsaturated fatty acids in HIV-infected patients taking potent antiretroviral therapy: a randomized prospective study. J Acquir Immune Defic Syndr. 2007;44:278-85.
14. Liu JP, Manheimer E, Yang M. Herbal medicines for treating HIV infection and AIDS. Cochrane Database Syst Rev. 2005;(3):CD003937.
15. Tuset M, Miro JM, Codina C, Blanco JL, Soy D. Interacciones de los fármacos antirretrovirales. In: Gatell JM, Clotet B, Podzamczer D, Miro JM, Mallolas J, editors. Guía practica del

SIDA: clínica, diagnóstico y tratamiento. Barcelona: Ed. Masson; 2002. p. 555-93.
16. Tuset M, Miro JM, Codina C, Martinez E, Garcia F, Mallolas J, et al. Interacciones de los fármacos antirretrovirales. AIDS Caber J. 1998;1:140-230.
17. Venkataramanan R, Ramachandran V, Komoroski BJ, Zhang S, Schiff PL, Strom SC. Milk thistle, an herbal supplement, decreases the activity of CYP3A4 and uridine diphosphoglucuronosyl transferase in human hepatocyte cultures. Drug Metab Dis. 2000;28:1270-3.
18. Scott GN, Elmer G. Update on natural product-drug interactions. Am J Health-Syst Pharm. 2002;59:339-47.
19. Gorski JC, Huang SM, Pinto A, Hamman MA, Hilligoss JK, Zaheer NA, et al. The effect of Echinacea (Echinacea purpurea root) on cytochrome P450 activity in vivo. Clin Pharmacol Ther. 2004;75:89-100.
20. Henderson L, Yue QY, Bergquist C, Gerden B, Arlett P. St John's wort (Hypericum perforatum): drug interactions and clinical outcomes. Br J Clin Pharmacol. 2002;54:349-56.
21. Hennessy M, Kelleher D, Spiers JP, Barry M, Kavanagh P, Back D, et al. St Johns wort increases expression of P-glycoprotein: implications for drug interactions. Br J Clin Pharmacol. 2002;53:75-82.
22. Wang Z, Gorski JC, Hamman MA, Huang SM, Lesko LJ, Hall SD. The effects of St John's Wort (Hypericum perforatum) on human cytochrome P450 activity. Clin Pharmacol Ther. 2001;70:317-26.
23. Wenk M, Todesco L, Krähenbühl S. Effect of St John's wort on the activities of CYP1A2, CYP3A4, CYP2D6, N-acetyltransferase 2, and xanthine oxidase in healthy males and females. Br J Clin Pharmacol. 2004;57:495-9.
24. Piscitelli SC, Burstein AH, Welden N, Gallicano KD, Falloon J. The effect of garlic supplements on the pharmacokinetics of saquinavir. CID. 2002;34:234-8.
25. Abrams DI, Milton JF, Leiser RJ, Shade SB, Elbeik TA, Aweeka FT, et al. Short-term effects of cannabinoids in patients with HIV-1: a randomized, placebo-controlled clinical trial. Ann Intern Med. 2003;139:258-66.