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The use of herbal medicine by AIDS patients from Hospital Universitário de Brasília, Brazil

[La utilización de hierbas medicinales por pacientes con SIDA del Hospital Universitario de Brasilia, Brasil]

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Abstract

An epidemiological study was carried out to verify the use of medicinal plants and herbal medicines by HIV-infected patients attended at Hospital Universitário de Brasília (HUB), and to evaluate the potential pharmacological interactions between prescribed antiretroviral medicines and such herbal preparations. A questionnaire was elaborated containing questions on the socio-demographic characteristics, time of diagnosis, how the patient discovered his disease, time of treatment with antiretroviral medicines, and the most frequent adverse effects, according to the patient. From the 128 interviewed patients, 52.3% claimed to be medicinal plants and/or herbal medicines users. Among patients using medicinal plant and/or herbal medicines, 77% did not inform the medical staff about this consumption practice. The results were higher than others similar reports. And several of the mentioned medicinal plants/ herbal medicine can potentially present important pharmacological interactions with anti-retroviral pharmacotherapy usually prescribed to the interviewed patients.

Keywords: AIDS, medicinal plants, herbal medicine, drug-herb interaction, ethnomedicine, anti-retroviral therapy.

Resumen

Un estudio epidemiológico fue realizado con el objetivo de evaluar la utilización y potencial interacción farmacológica entre hierbas/plantas medicinales y fármacos antiretrovirales prescritos a pacientes infectados con el VIH en el Hospital Universitario de Brasilia (HUB). Un cuestionario fue elaborado abordando preguntas sobre las características sociodemográficas, el tiempo de diagnóstico, como los pacientes se enteraron de sus enfermedades, el tiempo de tratamiento con los fármacos antiretrovirales, y los efectos adversos más frecuentes, de acuerdo a que informaran los pacientes. De un total de 128 pacientes entrevistados, 52.3 % informaron utilizar plantas e/o hierbas medicinales. Entre los pacientes utilizando plantas medicinales o hierbas, 77 % no informaron al equipo medico acerca de sus prácticas del uso de plantas/hierbas medicinales, porcentual este elevado se comparado a otros estudios. Muchas de las plantas/hierbas medicinales pueden potencialmente presentar importantes interacciones farmacológicas con la farmacoterapia antiretroviral usualmente prescrita a los pacientes entrevistados.

Palabras clave: SIDA, plantas medicinales, hierbas medicinales, interacción fármaco-planta, etnomedicina, terapia antiretroviral.

INTRODUCTION

A significant part of the traditional therapies used by communities, mainly from developing countries involves the use of plant extracts and their active principles(Farnsworth et al., 1985; Kong et al., 2003).

A research carried out in the United States (2002), detected a prevalence of 18.6% in the utilization of medicinal plants in alternative medical treatments, and it is 6.8% higher than 1997 (Tindle et al., 2005). In fact, the Organic Trade Association (OTA), in conjunction with Nutrition Business Journal, recorded United States sales of organic products at $14.7 billion and growing at 17% annually (Starling, 2006). A study performed in Europe involving cancer patients showed that the frequent use of medicinal plants was the most mentioned alternative treatment (Molassiotis et al., 2005). Similar results were found in Buenos Aires, with a percentage of 37.4% of utilization by the group researched (Franco and Pecci, 2003).

According to the Brazilian Phytotherapy Industry Association (ABIFISA), 82% of the Brazilian people use medicinal plant-based products, in agreement with the World Health Organization (WHO) data; and this consumption is based on little or absent scientific corroboration in relation to efficiency, safety and toxicity of the herbs (ABIFISA, 2002; Veiga et al., 2005). However, the defenders of the free and uncontrolled use of medicinal plants claim that they have already been tested and ratified by the long history of the human, and these facts make them

safe, effective and without significant side effects, common to synthesized products (De Smet, 2002, 2004; Ernst, 2004, 2006; De Smet, 2007). Thus, the apparent inoffensive image of herbal remedies encourages self-medication. The phytomedicine market is responsible for a yearly turnover of R$ 1 billion in all its productive chain and employs over than 100 thousand people in Brazil (ABIFISA, 2002).

Studies have indicated that patients with chronic diseases including those infected with the human immunodeficiency virus (HIV) make use of medicinal plants or herbal remedies to improve their quality of life and increasing their life expectancy (Ness et al., 1999; Duggan et al., 2001; Colebunders et al., 2003; Sugimoto et al., 2005; Taylor et al., 2006; Sharma et al., 2006). However, considering the large variety of medicines used in the anti-retroviral therapy, such combination would increase the possibility for the occurrence of drug-medicinal plant interactions that could promote reduction of the therapeutic effects and/or increase the anti-retroviral toxicity, as well as, the reduction on therapeutic effects and/or increase on the medicinal plants or herbal medicine toxicity. The aim of this study was verify the prevalence of medicinal plants and herbal medicines used by HIV-infected patients attended at Hospital Universitário de Brasília (HUB) and evaluate the potential pharmacological interactions between prescribed antiretroviral medicines and medicinal plants/herbal medicine.

MATERIALS AND METHODS

From a total of 199 patients with AIDS (Acquired Immunodeficiency Syndrome) attended at the Ambulatório do Hospital Universitário de Brasília (HUB) making regular use of anti-retroviral medicines from December 2002 to March 2004, a sample composed of 128 patients was calculated with confidence interval (CI) of 95%.

A transversal-type analytical epidemiological study was conducted to obtain data on the socio-demographic and clinical-epidemiological characteristics as well as information about the use of medicinal plants and/or herbal medicine by the participants of this survey. The statistical strategy was based on the analysis of variance (ANOVA) and in the chi-squared test. The results were considered as significant when $p<0.05$. The analysis of data was performed by using the Statistical Program for Social Sciences (SPSS) version 10.0.

The inclusion criteria were: age (not younger than 18 years of age); HIV infected; use of anti-retroviral drugs; ambulatory treatment. This research was previously submitted to approval from the Ethics Research Committee from the Faculdade de Ciências da Saúde, Universidade de Brasília.

The following background characteristics were used in the analysis: age, gender, marital status, educational level, employment situation, social interaction, monthly familiar income and address, time of diagnosis, how the patient discovered his disease, time of treatment with antiretroviral medicines, the pharmacotherapy used and the most frequent adverse effects, according to the patient.

About medicinal plants and/or herbal medicine, the following aspects were investigated: herbal medicine or medicinal plant used, form and time of utilization, purchase site, reasons and outcomes of the utilization and information to the medical staff in relation of this utilization.

Table 1. Socio-demographic characteristics of the 67 HIV-infected patients that reported the use of medicinal plants and/or phytomedicine

Parameters	**Number (%)**
Average age (± SD)*	38.8 (±9.49)
Male/ Female	44 (65.67)/ 23 (34.33)
Marital status	
Singles	38 (56.71)
Married or live matrimonially	22 (32.83)
Divorced/widowered	7 (10.5)
Educational level	
Illiterate	2 (3.0)
From 1 to 4 years of school	11 (16.24)
From 5 to 8 years of school	26 (38.8)
Graduated from High-School	23 (34.33)
Graduated from College	5 (7.5)
Monthly familiar income**	
< 1 minimum wage	1 (1.52)
Between 1 and 5 minimum wages	52 (78.79)
Between 6 and 10 minimum wages	7 (10.61)
> 10 minimum wages	6 (9.1)
Social interaction	
Family	53 (79.09)
Alone	10 (14.93)
Other (s) or in philanthropic institution	4 (6.0)
Residence area	
Urban	65 (97)
Rural	2 (3)

* SD – Standard Deviation

** Minimum wage in 03/01/2004 = US$100.00; one interviewed refused to inform the monthly familiar income.

Table 2 – Reasons for the use of medicinal plants and/or phytomedicine*

Reasons for the use of the Medicinal Plant/Herbal remedy	N (%)
Gastrointestinal disturbances	24 (38.1)
Pleasure or personal satisfaction	18 (28.6)
Pain and inflammation control or colds	8 (12.7)
Increase on the immunological response	6 (9.5)
Sedative and/or sleep inducer	3 (4.8)
Gastrointestinal disturbances and personal satisfaction	2 (3.2)
Weight reduction	1 (1.6)
Sedative and/or sleep inducer and due to gastrointestinal disturbances	1 (1.6)

*Some patients mentioned more than one reason.

Some interviewed reported the use of more than one medicinal plant or herbal medicine.

In addition, the medical staff was inquired with reference to their knowledge about properties of the herbal medicine, the frequency that their patients were using these ones, and the orientations provided to them. The physicians were also asked about their knowledge on possible interactions of medicinal plants and/or herbal medicine with the usual pharmacoterapy and the possible alterations on biological/pharmacological activities of these pharmaceuticals.

For the analysis of the pharmacokinetic and pharmacodynamic potential drug interactions between medicinal plants and herbal medicines and the prescribed pharmacotherapy, a research was performed using the following database: MEDLINE (1966-2007) and LILACS, pharmacology and medicinal plants textbooks.

RESULTS

From the 128 interviewed patients, 52.3% (95% CI; 40.3%-64.4%) claimed to be medicinal plants and/or herbal medicines users. The use in the last 4 years represented 25% (95% CI; 14.6%-35.4%) of consumption affirmatives and the use in the last year represented 18% (95% CI; 8.8%-27.2%). The socio-demographic characteristics of these patients are presented in Table 1.

Asked about why they initiate using medicinal plants, most of them reported that such habit is a familiar traditional practice (56, 6%; 95% CI 44.7%-68.5%). The recommendations received from relatives and friends represented 83.6% (95% CI; 74.7%-92.5%). The interviewed also accepted medical indication (3%), induced by TV programs, outdoor advertisements, radio, magazines and newspaper (4.5%).

The use of medicinal plants and/or herbal medicines, were associated to the reduction on the acute symptoms from adjacent pathologies [91.1% (95% CI; 84.3%-97.9%)]. Other reasons were: reduction on the disease symptoms (4.5%), cure for AIDS (2.9%) and to reduce of side and adverse effects caused by medications (1.5%) (Table 2).

When queried about the results obtained with the use of medicinal plants and/or herbal remedies, 86% (95% CI; 78.4%-94.8%) of them reported to have obtained positive results; 14% reported adverse effects or the lack of any result at all.

Patients using medicinal plant and/or herbal medicines usually did not inform the medical staff about this consumption practice [77% (95% CI; 67%-87%)]. Both patients who informed the medical staff about the use of medicinal plants and/or herbal medicines and those who did not inform the medical staff said had obtained positive results with this utilization (93% and 84%, respectively).

The most mentioned herbal medicine pharmaceutical forms were: decoction with water, decoction with milk, maceration, infusion, "garrafada" (a mixture of several medicinal plants on ethanol or cachaça), syrup and capsule.

In relation to the acquisition of the medicinal plant and/or herbal medicines, 61% (95% CI; 49.5%-75.9%) of users reported to have obtained the plant through own garden, 30% purchased the plant in free markets or known root shops and only 9% bought the plant in specialized pharmacies and drugstores.

Tables from 3 to 6 show the possible effects of cited medicinal plants and/or herbal medicines on the antiretroviral drugs action.

DISCUSSION

The obtained results were higher than others reports about HIV-infected patients using medicinal plants and/or herbal medicines (ranged from 20 to 40 %) (Kassler et al., 1991; Duggan et al., 2001; Colebunders et al., 2003; Sugimoto et al., 2005; Dhalla et al., 2006).

Table 3 – Plants and herbal remedies that can interact with antiretroviral drugs.

Latin name (vernacular)	Possible action	Interaction outcome	References
Ilex paraguariensis (erva mate) *Chenopodium ambrosioides* Bert. Ex Stend. (erva de santa maria); *Paullinia cupana* Kunth (guaraná); *Smilax* spp. (salsaparrilha); *Camellia sinensis* L. (chá preto)	Can promote unbalance of the acid-gastric buffer.	Cause increase of gastrointestinal discomfort and alteration in the ARV absorption	(Fetrow and Avila, 2000; Cowl, 2003; Philp, 2004; Simões et al., 2004; Taketa et al., 2004)
Symphytum officinale L. (confrei); *Sambucus nigra* L. (sabugueiro); *Hymenaea courbaril* L. (jatobá); *Gossypium barbadense* L. (algodão)	Can form a viscous gel of the mucilage and gastric solution.	Can reduce ARV absorption, either by the revetment of the gastric wall or by the adsorption of the medicine.	(Fetrow and Avila, 2000; Abdel-Kader et al., 2002; Cowl, 2003; Lima-Nishimura et al., 2003; Philp, 2004; Santos et al., 2004; Simões et al., 2004)
Matricaria chamomilla L. (camomila); *Mentha* spp. (hortelã)	Antispasmodic	Can reduce the motility of the gastrointestinal tract causing reduction of ARV absorption.	(Fetrow and Avila, 2000; Butterweck et al., 2004; delCastillo et al., 2004; Unger and Frank, 2004)
Aloe spp. (babosa)	Can increase the gastrointestinal peristaltic movement	Can promote changes in the ARV absorption due the increasing on the gastric emptying.	(Fetrow and Avila, 2000; Simões et al., 2004).
Allium cepa L.(cebola); *Eucalyptus globulus* Labill. (eucalipto)	Quercetin associates to the plasmatic protein in around 98%.	Can promote competition with ARV for the bond to the plasmatic protein.	(Havey, 1999; Fetrow and Avila, 2000; Philp, 2004; Simões et al., 2004)
Ilex paraguariensis (erva mate); *Serenoa repens* (saw palmetto); *Sambucus nigra* L. (sabugueiro); *Maytenus ilicifolia* Mart. ex Reiss (espinheira santa); *Paullinia cupana* Kunth (guaraná); *Camellia sinensis* L. (chá preto) *Eucalyptus globulus* Labill. (eucalipto)	Formation of tannin insoluble complexes with proteins.	Can increase the bioavailability of PI promoting higher bond to the plasmatic protein.	(Fetrow and Avila, 2000; Izzo and Ernst, 2001; Cowl, 2003; Ohsaki et al., 2004; Philp, 2004; Simões et al., 2004; Taketa et al., 2004)
Matricaria chamomilla L. (camomila) *Mentha* spp. (hortelã) *Uncaria tomentosa* (Willd. Ex Roem. & Schult.) DC. (unha de gato)	Inhibition of CYP450, *in vitro*.	Can increase the ARV bioavailability and/or toxicity.	(Fetrow and Avila, 2000; Williams, 2001; Cowl, 2003; Butterweck et al., 2004; Philp, 2004; Simões et al., 2004)
Allium sativum L. (alho)	Induction of CYP450.	C_{max} SQV: reduction of 54% AUC SQV: reduction of 51% C_{max} PI: reduction	(Santos et al., 2004; Santos and Boullata, 2005)
Allium cepa L. (cebola)	Induction of CYP450.	C_{max} and AUC of PI: reduction	(Havey, 1999)

ARV=antiretroviral; PI=Protease inhibitor; CYP450 = cytochrome P450; PI=protease inhibitors; C_{max} = maximum concentration; AUC=area under curve; SQV=saquinavir

Table 4 – Plants and phytomedicines that can cause side effects synergism

Latin name (vernacular)	Possible action	Interaction outcome	References
Peumus boldus Molina (boldo do chile)	Anticholinergic action	Can increase neuropsychiatric EFV side effects.	(Fetrow and Avila, 2000).
Symphytum officinale L. (confrei)	Hepatotoxicity	Can increase NRTI, NNRTI and PI-induced hepatic damage.	(Fetrow and Avila, 2000; Philp, 2004; Simões et al., 2004)
Mentha pulegium L. (poejo)	Hepatotoxicity	Can increase NRTI, NNRTI and PI-induced hepatic damage.	(Fetrow and Avila, 2000; Lorenzo et al., 2002)
*Mikania glomerata Spreng.(*guaco*);*	Formation of chelate by cumarin and iron ions	Can promote pancytopenia with NRTI, NVP and PI.	(Fierro et al., 1999)

EFV=efavirenz; PI=protease inhibitors; NRTI= nucleoside analogous reverse transcriptase inhibitors; NNRTI= nucleoside non-analogous reverse transcriptase inhibitors; ↑ = increase.

Table 5 – Plants and their phytochemicals: possible interactions mechanisms

Latin name (vernacular)	Phytochemicals	Interaction outcome	References
Ilex paraguariensis (erva mate); *Paullinia cupana* Kunth (guaraná); *Camellia sinensis* L. (chá preto).	Psychoactive substances	Can increase neuropsychiatric EFV side effects.	(Fetrow and Avila, 2000; Cowl, 2003; Philp, 2004; Simões et al., 2004; Taketa et al., 2004)
Operculina alata (Ham) Urban. ("Batata de Tiú")	Psychoactive substances	Can increase neuropsychiatric EFV side effects.	(Simões et al., 2004)
Myristica fragrans Houtt (nutmeg)	Psychoactive substances	Can increase neuropsychiatric EFV side effects.	(Fetrow and Avila, 2000; Cowl, 2003; Simões et al., 2004)

EFV=efavirenz;

Our research revealed that the recommendations for the use of medicinal plants and/or herbal remedies were usually obtained from relatives (great-grandparents, grandparents, parents, brothers, etc) and friends; only 3% of them from medical prescription. In another study, realized in Thailand, that evaluated the use of medicinal plants by HIV-infected patients, the recommendations obtained from relatives and friends represented 14% and under medical prescription represented 36% of cases (Sugimoto et al., 2005).

In a quest performed with Brazilian cancer patients the phytotherapy, when used alone, represented 71.64% of the non-conventional therapeutic modalities reported by patients, being also recommended by relatives and friends in 80.6% of cases (Elias and Alves, 2002). The same data obtained in relation to the prevalence and recommendation for the use of medicinal plants and herbal remedies were also observed in pre-surgical patients from Lenox Hill Hospital, New York, being the prevalence of 57% for the use and 63% for recommendations received (Adusumilli et al., 2004).

Overall, 53 types of preparations involving medicinal plants were identified. From these, 6 (11.32%) could not be identified due to the lack of access to the medicinal plant or herbal medicine because the interviewed could not make a clear description of the plant or herbal medicine, or because the patient used popular nomenclature for different species employed at distinct pathological conditions. Also, it was not possible identifying components present in preparations as "garrafadas" and others herbal complex mixtures (usually powdered) presenting no label containing the product description. These results are in agreement with a study performed with HIV/AIDS patients from University of California, San Francisco: from 22% of patients reporting the use of medicinal plants during three months preceding the interview, 24% could not identify which medicinal plant (s) they were making use of (Kassler et al., 1991).

The lack of quality, unknown origin and misidentification of *in natura* medicinal plants, in addition to the adulteration of herbal medicines with heavy metals, hormones, stimulants, anti-inflammatory agents and other drugs, are well

reported problems involved with herbal medicine (Camargo, 1998; Winslow and Kroll, 1998; Corns, 2003; Betti and Thomsen, 2005; Grollman, 2005; Gomez et al., 2007; Latif and Rahman, 2007).

These aspects must be carefully observed, once in the present study, 91% of the *in natura* medicinal plants mentioned by the interviewed were obtained through own plantation garden, free markets and root shops. Such practice may result in the use of potentially toxic species by a mix up due to similarities in relation to the macroscopic characteristics, or popular name of the medicinal species. Another recurrent problem is the contamination of herbs or herbal medicines by fungi and pathogenic bacteria that may promote toxic reactions, being also responsible for alterations in the expected effects of these medicines (Themboa et al., 2007).

HIV-infected patients under drug therapy use anti-retroviral triple scheme and, no rare, additional medicines for the treatment of opportunistic infections. Medicinal plants and/or herbal medicines are composed of several chemical components (Taylor et al., 2006; Tirona and Bailey, 2006; De Smet, 2007; Langlois-Klassen et al., 2007), thus, the association anti-retroviral therapy/medicinal plants may increase the risk of developing adverse drug reactions (Zhou et al., 2007). The physicians and the patients must perform a careful evaluation in relation to this potential risk, before starting the phytotherapy (Foster et al., 2003; Foti et al., 2007).

Pharmacokinetic interactions may reduce the drug bioavailability and hence its efficiency or increase its bioavailability resulting in possible increased toxicity. The pharmacokinetic interactions presented in this work were mainly related to the medicine absorption, bonding to the plasmatic protein and induction or inhibition of the drug in the cytochrome P450 (CYP) (Foti et al., 2007).

Among plants and herbal medicines used by the interviewed, the phytochemicals are worth of emphasis because they may change the antiretroviral drugs absorption, reducing the area under plasma concentration *vs* time curve.

Absorption alterations that promote the reduction of the drug efficiency, antiretroviral included, may be caused by plants and/or herbal medicines containing saponins (Castilla et al., 2006), such as *Ilex paraguariensis*, *Chenopodium ambrosioides*, *Paullinia cupana*, *Smilax* spp and *Camellia sinensis*. The mucilage present in *Symphytum officinale*, *Sambucus nigra*, *Hymenaea courbaril* and *Gossypium barbadense*, can form a viscous thin layer on the gastrointestinal mucosa causing reduction on the antiretroviral drug absorption, or through the revetment of the gastric wall or through the absorption of the medicine molecule (Haq, 2004) .

Medicinal plants with antispasmodic action as *Matricaria chamomilla* and *Mentha* spp. reduce the motility of the gastrointestinal tract, thus reducing the antiretroviral medicines absorption. In fact, *Mentha* spp reduces total gastrointestinal transit or gastric emptying, decreases the basal tone in the gastrointestinal tract, and inhibits potassium depolarization-induced responses in the intestine (Rodriguez-Fragoso et al., 2008).

The anthraquinones present in aloe can increase the peristaltic movements; therefore, can reduce the bioavailability of antiretroviral medicines. (Laitinen et al., 2007). Quercetin, widely found in nature and present in *Allium cepa* and *Eucalyptus globulus*, binds to the plasmatic proteins in around 98% and when administered with other medicine with high binding to the plasmatic protein, may lead to a pharmacological competition, and this interaction may form both a dislocated drug and a dislocating drug (Havey, 1999; Philp, 2004; Farkas et al., 2007). Thus, herbal medicines or large amounts of food containing onion or eucalyptus when used concomitantly with efavirenz, which present binding percentage to the plasmatic protein higher than 99% (deMaat et al., 2003), may promote a competition for this binding. It is known that, in this case, in other words, if the efavirenz is dislocated, its excitability symptoms in the central nervous system would become exacerbated. Considering the results obtained, it was verified that 28.1% of patients used zidovudine, lamivudine and efavirenz as therapeutic scheme and that *A. cepa* is a seasoning with large presence in the Brazilian cookery, it becomes crucial to inform patients on their concomitant use with the pharmacotherapy.

The tannins present in *I. paraguariensis*, *Serenoa repens*, *S. nigra*, *Maytenus ilicifolia*, *E. globulus*, *P. cupana* and *C. sinensis* can form insoluble complexes with plasmatic proteins (Rivera et al., 2006), leading to an increase on the bioavailability of protease inhibitors, once this antiretroviral class presents high binding to the plasmatic protein. The increase on the bioavailability of this medicine class may lead to exacerbation on its side effects, among them, the blood stasis (Izzo and Ernst, 2001; Ohsaki et al., 2004; Philp, 2004; Taketa et al., 2004; Izzo, 2005).. The increase on the efavirenz side effects may also

occur as a result of its increased bioavailability (deMaat et al., 2003).

Other clinical relevant pharmacokinetic interactions can occur in the cytochrome P450 (CYP450). Alterations on the medicine bioavailability or efficiency may occur with the inhibition or induction of the enzymatic metabolism, respectively. The CYP450 is the isoform involved in the metabolism of at least 50% of drugs including the protease inhibitors (antiretroviral drugs). The CYP3A4 is more quantitatively expressed in the liver and on the intestine wall (Harris et al., 2003).

Among medicinal plants/phytomedicine that can interact with CYP450, increasing the bioavailability or toxicity of antiretroviral drugs, *Uncaria tomentosa Matricaria chamomilla* and *Mentha* spp. stand out (Foster et al., 2005). An *in vitro* study showed the *U. tomentosa* inhibitory activity in the CYP3A4 (57%), CYP2D6 (13%) and CYP2C9 (11%). *Matricaria chamomilla*, in turn, also presented inhibitory activity in CYP3A4 (57%), CYP2D6 (54%) and CYP2C9 (61%) (Foster et al., 2003).

The essential oil from *Matricaria recutita* L and the constituents *cis*-spiroether, *trans*-spiroether, alpha-bisabolol, and chamazulene can promote inhibition of CYP450 enzymes (CYP1A2, CYP2C9, CYP2D6, and CYP3A4) *in vitro* (Ganzera et al., 2006).

Another *in vitro* study showed the *Mentha* spp. inhibitory activity in the CYP450 (Unger and Frank, 2004). The concern about action of medicinal plants or herbal medicines on CYP is increasing, meanly at countries when the use of medicinal plants sometimes is the one therapeutical resource (Mills et al., 2005).

Antiretroviral drugs belonging to the nucleoside non-analogous reverse transcriptase inhibitors class and protease inhibitors present hepatic metabolism, especially by isoforms CYP3A4, CYP2B6, CYP2C9, CYP2C19 and CYP2D6 (deMaat et al., 2003; Foster et al., 2005) and the concomitant use of *U. tomentosa*, *M. chamomilla* and *Mentha* spp with the class mentioned above may lead to an increase on their bioavailability/toxicity. In the same way medicinal plants and/or herbal medicines may also induce their metabolism in this enzymatic system, reducing the antiretroviral medicine efficiency. Among the mentioned plants/herbal remedies, garlic and onion are included.

In a study conducted in humans aliin, present in *Allium* spp. promoted inductive activity of the CYP450 enzymatic system, causing reduction on the saquinavir maximum concentration in 54% and its area under curve in 51% (Piscitelli et al., 2002). This compound is also present in the *A. cepa* (Havey, 1999), suggesting the same inductive activity on CYP450 enzymatic system.

In relation to pharmacodynamic interactions, the present study identified some medicinal plants/herbal medicines can promote side effects synergism if administered concomitantly with some antiretroviral medicines.

Psychoactive substances present in *I. paraguariensis*, *Operculina alata*, *Myristica fragrans* and *C. sinensis* may enhance the efavirenz-induced neuropsychiatric side effects. The *Peumus boldus*, due to its anticholinergic action, also can enhance the efavirenz-induced stimulation of the central nervous system.

Antiretroviral drugs belonging to the nucleoside analogous reverse transcriptase inhibitors and nucleoside non-analogous reverse transcriptase inhibitors classes and the protease inhibitors cause increases on the alanine transaminase (ALT) and aspartate transaminase (AST) hepatic expression, indicating a chronic or acute hepatotoxicity. *Symphytum officinale* and *Mentha* (Fetrow and Avila, 2000; Lorenzo et al., 2002; Philp, 2004) are hepatotoxic and when administered with antiretroviral drugs may enhance hepatic injuries.

Zidovudine, didanosine, estavudine, lamivudine, tenofovir, nevirapine, indinavir, lopinavir, nelfinavir, ritonavir and saquinavir produce hematological substances causing pancytopenia. This side effect is exacerbated with the concomitant administration of *Mikania glomerata*, due to its iron ions chelating action.

Interactions involving phytochemicals and conventional drugs give the wrong impression of being less frequent and severe than drug-drug interactions. This induces the false idea that plants and/or phytomedicine present irrelevant pharmacological profile and that their actual pharmacological potential should not be taken into account. Such fact leads to the occurrence of misidentification and lack of notification about the adverse effects of plants and herbal medicines that, in addition to a small number of scientific researches about them, contribute to the maintenance of the condition of being inappropriately used by the population, with increased risk to the users' health. In fact, the market of largely unregulated herbal medicines presents significant risks to public health.

In May 2006, the Brazilian Ministry of Health published a Government announcement that regulates

integrative and complementary practices in the Brazilian Public Health System (Sistema Único de Saúde - SUS), including phytotherapy. Thus, the capability of researches on the safety in relation to the use of this therapeutic arsenal should be encouraged, and information in relation to cautions of their use should be given to patients. However, it was observed that the parcel of patients (77.6%) who reported not to inform the medical staff on the use of medicinal plant/herbal remedy is relevant, corroborating previous works (Eisenberg et al., 1998; Adusumilli et al., 2004; Sharma et al., 2006), which reported that patients seldom inform voluntarily to the medical team on this practice.

Although not included in the questionnaire applied, patients explained the reasons why they did not disclosure to the medical staff on his habit of using plants or herbal medicines. The fear of a negative reaction by the physician was relevant reason presented by them.

The lack of scientific corroboration and the misconceptions about herbal medicine such "if it does not do any good, it will not do any bad either", among other explanations, were the most heard responses from the medical staff in relation to patients who reported this practice.

On the other hand, according to results from survey performed with the medical staff responsible for the care of these patients, it was verified that among the physicians inquired, 66.67% reported that routinely ask the patient about the use of medicinal plants/herbal remedies, but only half reported to provide information to the patient on this habit. However, the opinion in relation to the high interference level that medicinal plants and/or herbal remedies may cause to the pharmacotherapy was unanimous.

When inquired in relation to some information on medicinal plants and/or herbal medicines, only 33% of the physicians provided the right answer for more than half of the questions about differences between medicinal plant and herbal medicines and their biological/pharmacological activity.

CONCLUSION

Considering the wide and growing use of medicinal plants and/or herbal medicines, researches focuses on phytochemical identification, with emphasis on their pharmacological effects, as well as their action mechanisms, efficiency and safety should be stimulated. The physicians and patients must perform a careful evaluation about the potential risks, before starting the phytotherapy (Foster et al., 2003)

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