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Possible Adverse Reactions to Herbal Products: A Study with Individuals Who Resort To Popular Medicine in the City of Diadema, SP, Brazil

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The present study aimed to investigate the occurrence of adverse reactions (ADRs) related to herbal products (HPs), which are purchased over-the-counter for self-treatment, reported by 100 users. Samples of the HPs related to those ADRs were purchased for their pharmacobotanical identification. The ADRs reported were evaluated based on specialized literature and were analyzed according to causality into probable (PR), possible (PO), unrelated (UR) or unclassifiable (UC); according to expectance into unexpected adverse reaction (UNEX) and expected adverse reaction (EX); seriousness into serious adverse event or reaction (S) and non-serious (NS); and severity into mild (MI), moderate (MO) and severe (SE). Among 100 interviews, five complaints of ADRs were reported in relation to HPs: *Senna alexandrina*, with a report of cramps (PR; MI; EX; NS); *Camellia sinensis*, associated with tachycardia (PO; MI; EX; NS); *Bauhinia sp.*, a strong allergic reaction that led to hospitalization (UC; MO; UNEX; S); *Picrasma crenata*, with several symptoms and hospitalization (UR; MO; UNEX; S); and 21-herb tea, related to an allergic reaction (UC; MI; EX; NS). The strategies used in this study allowed us to carry out an analysis of ADRs attributed to HPs. This analysis could serve as a model in the study of similar cases. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords: pharmacovigilance; adverse drug reaction; herbal products; herbal teas; herbal drugs; folk medicine.

INTRODUCTION

There are several legal definitions for herbal products (HPs). In this study, HPs involve the following definitions: *Herbal Drugs*, which are mainly whole, fragmented or broken plants, parts of plants, algae, fungi or lichen, in an unprocessed state, usually in dried form but sometimes fresh; and *Herbal Teas* which consist exclusively of one or more Herbal Drugs intended for oral aqueous preparations by means of decoction, infusion or maceration (British Pharmacopoeia, 2012).

Wong and Castro (2003) mention five factors that might be related to the toxicological aspects of phytomedicine medications: (i) environmental factors (edaphoclimatic, ecological interaction, nutrition); (ii) drug interaction (synergisms and antagonisms) with phytomedicine and synthetic medications; (iii) possible accidental substitution for another plant that can be toxic; (iv) lack of information about the toxic, acute or chronic effects of the phytomedicine medication; (v) substitution by another phytomedicine medication without medical guidance.

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Cases of adverse drug reactions (ADRs), intoxications and contaminations are often described in the scientific literature, reinforcing the need of interdisciplinary studies to minimize the risk those products might entail (Veiga, 2008). The World Health Organization (WHO, 2002) defines ADRs to medication as a harmful, non-intentional reaction that might happen after individuals have ingested the usual doses.

It is also important to consider the fact that the present model of pharmacovigilance and its investigation methods are well developed in relation to synthetic medications. However, the application of those methods to phytomedicine and other HPs poses challenges beyond the reach of the methods used for synthetic medications (Barnes, 2003). Considering the concept of ADR described above, this challenge is even greater in the case of herbal medicines or HPs, since in most cases, there are no studies showing at what doses they are effective and safe.

The objective of the present study was to investigate the occurrence of ADRs related to the use of HPs, products purchased over-the-counter (OTC) for self-treatment, reported by users in an area of informal trade of HPs in the city of Diadema, São Paulo, Brazil. The complaints reported were considered evidence for the formulation of the pharmacological hypothesis of ADRs. Additionally, we carried out pharmacognostic analyses of the HPs sold in that area which presented ADRs, in order to corroborate the authenticity of the complaints.

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METHODS

The Committee of Ethics in Research of UNIFESP approved the project (CEP 1672/07). All volunteers signed a Free Informed Consent Form. The present study had an observational and descriptive design (Michael *et al*., 2000) and involved the participation of an intentional sample (Bernard, 1988), composed by 100 users of HPs (products they purchased OTC for self-treatment), who were interviewed by one of the authors (Soares Neto, JAR.) between January 15th and May 30th, 2009. The interviews were based on a form developed in for our previous study (Soares *et al*., 2010) and were carried out in the area of informal trade of HPs.

Area of study and field work. The field work was carried out in the city of Diadema, located 17 km away from the city of São Paulo (SP). Diadema has a Human Development Index – cities (HDI –C) of 0.79 (PNUD, 2000). In order to develop the field work, we used semi-structured interviews (Bernard, 1988).

The interviewees (HPs users) were randomly approached in a place where HPs are sold (informally) and invited to participate in the study. As the inclusion criteria, they had to be over 18 years old. They were approached when buying HPs, and their data were recorded in the interview form. The questions regarded possible complaints (ADRs) related to the use of HPs; their consumption (where they purchased; reason for using; form of preparation; how long they had been using, combined use with other HPs or medications) and personal data (age, gender and education). The interviewer was trained prior the actual interviews to choose the best way to approach the volunteers and to use words that would be easily understood, due to the cultural and social diversity of the users.

Pharmacognostic study. As regards the HPs reported in the interview, that is, those related to ADRs, we purchased samples to perform the pharmacognostic analysis. Some of them had their botanical identification determined according to pharmacopeias or specialized literature, while others did not. Their macroscopic characterization was done with the naked eye and also with the aid of a stereoscopic magnifying glass Wild Heerbrugg®. The anatomic characterization of the samples was performed through cuts prepared with the rehydrated HPs (Berlyn and Miksche, 1976). The transversal and longitudinal cuts of the samples were performed manually or with the aid of a microtome, and later treated with chemical reagents adequate to each kind of structure (Sass, 1951). The cuts used in the documentation were dyed with solutions of safranin and Astra blue (Roeser, 1962). They were analyzed with the aid of an Olympus® microscope, and the photographs were taken by a Nikon® photomicroscope. Physicochemical analyses complemented the evaluation.

Bibliographical review. For the species studied, we ran a bibliographical search in scientific journals available in the following databases: Micromedex; Poisonous Plant Database; Scopus; SciELO; Pubmed; BVS; Capes Journals; FDA Consumer; Science Direct; SpringerLink. The key words used for the search were: Adverse reactions; Adverse events; Side effects; Pharmacovigilance; Toxicology; Intoxication; Hospitalization and Death, limited to publications related to humans. This search enabled us to create a small monograph for each species, when the botanical identification was possible by means of pharmacognosy, containing the following data: botanical, ethnopharmacological, pharmacological, toxicological and ADRs.

Classification and categorization of suspected adverse reactions. Based on the data obtained in the present study along with those described in scientific journals, we were able to analyze the ADRs reported by the individuals in our sample according to the following classification and categories, respectively: (i) causality into probable (PR), possible (PO), unrelated (UR) or unclassifiable (UC); (ii) expectance into unexpected adverse reaction (UNEX) and expected adverse reaction (EX); (iii) seriousness into serious adverse event or reaction (S) and non-serious adverse event or reaction (NS) (WHO, 2000, 2012a) and finally (iv) severity into mild (MI), moderate (MO), severe (SE) or lethal (LT) (Rawlins and Thompson, 1991).

According to the WHO (2012b), a 'serious' adverse event or reaction is any untoward medical occurrence that at any dose: results in death; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is life-threatening. The absence of any of those conditions is considered a 'non-serious' adverse event or reaction. In order to prevent misunderstanding, the WHO emphasizes the care in the distinction between seriousness and severity. 'Severe' is used to describe the intensity (severity), while seriousness, which is based on patient/event outcome or action criteria, serves as a guide for defining regulatory reporting obligations (WHO, 2012b).

RESULTS AND DISCUSSION

In spite of the difficulties to carry out a survey on suspected ADRs in an area of informal trade of HPs, there was a clear cooperation of the salespersons and adherence of all the interviewees. On the other hand, there is an ideological discourse against official medicine in those environments, where the use of HPs is also a form of resistance.

We observed that the users interviewed were predominantly female. Most of them reported being satisfied with the use of 'medicinal plants', which shows their therapeutic and cultural importance. Some of the users interviewed declared being purchasing the herbs at that moment for some family member, or that they had made very little use of HPs, but had felt motivated to use them as a result of information on their benefits through television or

friends/family members. For the HPs users who did not report any ADRs, some of the justifications were:

- '*I have always used medicinal plants*, *and you have to get the children used to them since they are little. The plants have always worked for me*, *and I only go to the doctor if there's no other way. The medicine you buy at drugstores helps you on one hand*, *but harms you on the other*'.
- '*I make little use of medicinal plants*, *but they always produce the expected effect; the physicians tell me to use them*'.
- '*I always use medicinal plants and also conventional medicines*, *but I think it's better to use medicinal plants; we trust that it will produce the expected effect*'.
- '*A friend indicated this plant to me*, *but medicinal plants never do you any harm; my grandfather also used them*'.

Our results showed the importance of popular medicine and the use of HPs for the interviewees, but they do not support the belief of the perfect safety of those products. The ideologies of popular medicine, which include the discourse about official medicine, might interfere in the correlation and/or acceptance of the problems related to HPs, and their consequent report to health professionals and even to the interviewer of this research. This might suggest that perhaps only the most severe ADRs were reported.

In the following tables, regarding the herbal tea infusion of senna, the dried leaflet of *Senna alexandrina* P. Miller (Fabaceae) (Table 1); Tea infusion of black tea, the fermented dried leaf of *Camellia sinensis* (L.) Kuntze (Theaceae) (Table 2); herbal tea infusion of 'pata-de-vaca' fresh leaves *Bauhinia* sp (Fabaceae) (Table 3); herbal tea decoction of bitter wood of *Picrasma crenata* Engl. In Engl. & Prantl (Simaroubaceae) (Table 4); and the Herbal tea infusion of 21- herb tea mixture (Table 5), we describe the personal data of the users and the complaints five out of 100 users had about the HPs they used. We also present the classification of the suspected ADRs as to their causality, severity, expectance and severity, as well as the results obtained in the pharmacognostic analysis of the authenticity of the plants.

Senna (Table 1) corresponds to the leaflets of the species *Senna alexandrina* P. Miller. (Fabaceae), rich in anthraquinone, which has a laxative action. They contain 1 to 3% of hydroxyanthracene derivatives, predominantly sennosides A and B. The daily dose

Table 1. Data collected for the analysis and classification of a possible ADR to senna. Diadema - SP, Brazil, 2009

HP		Data
Senna	Personal data	Female, 37 years old, complete middle school
	Place of purchase	Informal trade area
	Reason for using	Constipation
	Complaint reported	Had a strong and persistent stomachache, with cramps
	Form of preparation	Dried leaflet infusion: 3 min. in boiling water; one tablespoon (about 3 g) for one glass (250 mL)
	Duration of use	One glass (250 mL) immediately after preparation, only once
	Combined use with other HPs or medicines	She reported not making combined use with other medications
	Methods of analysis	**Results**
	Identification	*Senna alexandrina* P. Miller. (Fabaceae)
	Literature	Hydroxianthracenic derivatives: laxative action
	Categorization of suspected ADR	Causality: probable
		Severity: mild
		Expectance: expected adverse reaction
		Seriousness: non-serious

Table 2. Data collected for the analysis and classification of a possible ADR to black tea. Diadema - SP, Brazil, 2009

HP		Data
Black tea	Personal data	Female; 59 years old; complete high school
	Place of purchase	Supermarket
	Reason for using	As food
	Complaint reported	Tachycardia one hour after drinking it
	Form of preparation	Dried leaf infusion: 3 min in boiling water; one teabag (approximately 1.8 g) for one cup of water
	Duration of use	One teabag only once, drunk immediately after preparation
	Combined use with other HPs or medicines	One pill of 25 mg of hydrochlorothiazide and amiloride for high pressure
	Methods of analysis	**Results**
	Identification	*Camellia sinensis* (L.) Kuntze (Theaceae)
	Literature	Caffeine: stimulation of the cardiac muscle / heightened sensitivity
	Categorization of suspected ADR	Causality: possible
		Severity: mild
		Expectance: expected adverse reaction
		Seriousness: non-serious

Table 3. Data collected for the analysis and classification of a possible ADR to 'pata-de-vaca'. Diadema - SP, Brazil, 2009

HP		Data
"***Pata-de-vaca***"	Personal data	Female, 57 years old, finished the 1st year of high school
	Place of purchase	Picked from a tree on the street (Diadema)
	Reason for using	To treat diabetes
	Complaint reported	Allergic reaction all over her body; reported feeling her eyes and her mouth '*getting locked*' and having a feeling of death. Her mother had the same reactions after drinking the same tea. Both had to be hospitalized
	Form of preparation	Fresh leaves infusion: 3 min. in boiling water; six leaves (6 g) for 1 L of water
	Duration of use	Two glasses (total of 500 mL) immediately after preparation, only once
	Combined use with other HPs or medicines	She reported not being using other substances at the moment, but using them regularly to detoxify from the effects of synthetic medications
	Methods of analysis	**Results**
	Identification	*Bauhinia* sp. (Fabaceae)
	Literature	No similar reports in the phytomedicine literature. ADR not reported yet?
	Categorization of suspected ADR	Causality: Unclassifiable Severity: moderate Expectance: unexpected adverse reaction Seriousness: serious

suggested for the ingestion of senna is between 15 and 30 mg of anthracene (ESCOP, 2003). In Brazil, the legislation allows 10–30 mg (ANVISA, 2008).

The laxative action of senna has been documented for centuries, and the plant is used all over the world in many industrialized products (Freitas, 2007). Similarly,

Table 4. Data collected for the analysis and classification of a possible ADR to bitter wood. Diadema - SP, Brazil, 2009

HP		Data
Bitter wood or "*pau-tenente*"	Personal data	Female, 60 years old, finished the 3rd year of elementary school
	Place of purchase	Informal trade area
	Reason for using	To treat diabetes
	Complaint reported	After one week of using the preparation, she was hospitalized with tachycardia, feeling of loss of consciousness, high blood pressure and diabetes, according to the hospital identification. One week after being discharged from the hospital, she used the preparation again for another week and consequently had to be taken to the hospital again with the same condition (she was sternly warned by the physicians on both occasions)
	Form of preparation	Wood decoction: 10 min in boiling water; one tablespoon (about 3 g) for one glass of water (250 mL). She had that dose three times a day, using it immediately after preparation
	Duration of use	The actual period of use was two weeks, but the complete period (from the first day of use and hospitalization to the last day of recovery) was one month
	Combined use with other HPs or medicines	Not reported. Note: it was not possible to confirm whether she was pre- diabetic
	Methods of analysis	**Results**
	Identification	*Picrasma crenata* Engl. In Engl. & Prantl (Simaroubaceae)
	Literature	Discreet hypoglycemiant and anti-gastric ulcer effects (few studies have been published)
	Categorization of suspected ADR	Causality: unrelated Severity: moderate Expectance: unexpected adverse reaction Seriousness: serious

Table 5. Data collected for the analysis and classification of a possible ADR to 21-herb tea. Diadema - SP, Brazil, 2009

HP		Data
21 –herb tea*	Personal data	Female, 27 years old, finished high school
	Place of purchase	Informal trade area
	Reason for using	To lose weight
	Complaint reported	Allergy all over her body, with a rash
	Form of preparation	*21- herb tea infusion* (mixture): About 1 to 3 min in boiling water; three tablespoons (about 9 g) for 1 L of water
	Duration of use	Used the whole preparation in one day
	Combined use with other HPs or medicines	Not reported
	Methods of analysis	**Results**
	Identification	Finely powdered greenish-brown product Microscopic characterization unviable
	Literature	Asteraceae family: sesquiterpene lactones (produce allergic reactions in sensitive patients)
	Categorization of suspected ADR	Causality: Unclassifiable Severity: mild Expectance: expected adverse reaction Seriousness: non-serious

the ADRs related to the mechanism of action of the plant are also known, particularly the promotion of a mild abdominal discomfort and cramps. Its prolonged use might cause diarrhea with electrolytic unbalance and atonic intestinal muscles (Hietala *et al*., 1987). The event reported in this study (cramps and stomachache together) might be related to the dose used, a possibility that led us to evaluate the amount the patient ingested. One tablespoon of senna, the dose ingested by the interviewee, should supply around 5 g of the HP, corresponding to 50 to 150 mg of anthracenes (according to the range of possible active constituents of the plant, that is, 1 to 3%). This amount is above the maximum daily dose recommended, which is 30 mg of anthracenes. The U.S. Food and Drug Administration monograph (1985) establishes that the oral dosage of senna laxative range for adults and children 12 years of age and over is 12 to 50 milligrams once or twice daily, which does not characterize overdose. Therefore, such increase in the dose might justify the occurrence of the stomach pain and cramps reported by the patient. According to the causality relation of WHO-Art, since there was no report of combined use with other medication, the present case fits the concept of side effect. Relation of causality: probable. Severity: mild. Expectance: expected adverse reaction. Seriousness: non-serious.

The second case (Table 2) is related to black tea - *Camellia sinensis* (L.) Kuntze (Theaceae), whose leaves are used worldwide in the preparation of stimulant beverages due to the presence of caffeine. These leaves can be found in several forms, known as black tea, green tea and oolong, among others. Black tea contains a complex mixture of products of enzymatic oxidation of catechins, among which benzotropolones stand out (Sharangi, 2009).

The stimulation of the cardiac muscle is among the main pharmacological actions of caffeine as a result of the stimulation of beta-adrenoreceptors (Lane *et al*., 1994; Matsuo *et al*., 2006). This effect might justify the reaction reported by the patient in the present research (tachycardia). The concentration of xanthines in tea ranges from 1 to 4%, considering caffeine and theophylline (Yang *et al*., 2007). In terms of doses, one standard commercial teabag contains, on average, 1.5 to 2.0 g of the torn plant, an amount that could supply about 50 mg of xanthines for a 200 mL cup, the dose used by the interviewee.

According to Grobbe *et al*. (1990), no one should ingest more than 250 mg of caffeine a day. The dose ingested by the patient was well below this daily limit and therefore would not account, on principle, for the reaction reported. On the other hand, there might have been a concomitant ingestion of coffee within a short period of time, causing an overload of caffeine in her system. Studies point that food, such as coffee, tea, chocolate and sodas of the cola type, is responsible for the major sources of caffeine; moreover, it is also present in medicines (Souza and Sichieri, 2005). Another possibility is that the interviewee might be highly sensitive to this ingredient, to the point of feeling tachycardia with only the dose of a teabag, a fact that was reported in the literature we consulted (Boulenger *et al*., 1984).

In relation to synthetic medicines used concomitantly by the patient, composed by a hydrochlorothiazide and amiloride, which is considered to have diuretic effects, and therefore is prescribed to hypertensive patients, we did not find any data or studies that suggest interactions between black tea and this medicine. A synergic diuretic effect between those two conventional medications and the caffeine present in the tea might cause a hypotensive event. This possibility, however, does not show a clear relation with the tachycardia reported by the patient. Therefore, according to causality relation of WHO-Art, we consider that the reaction reported for black tea was a side effect of caffeine in a sensitive patient. Relation of causality: possible. Severity: mild. Expectance: expected adverse reaction. Seriousness: non-serious.

Considering the popular name 'pata-de-vaca' (Table 3), the phytomedicine literature refers us to species of the genus *Bauhinia* (Fabaceae), mainly the *B. forficate* Link. (da Cunha *et al*., 2010), and others of less importance but also used for their hypoglycemiant properties. In this context, Fuentes *et al.* (2004) report *B. candidans* Benth., used in Chile and in the South of Brazil for its diuretic properties and to reduce glycemia and cholesterol. *B. ungulata* L., informally known as mororó (Morais *et al*., 2005) is popular in the Northeast of Brazil.

Regarding the allergic reaction of the patient (Table 3), an event also observed in her mother, there are no similar reports in the extensive phytomedicine literature we consulted in search of this type of reaction, taking into account the genus, without specifying the species. On the other hand, according to data published by the *Agência Nacional de Vigilância Sanitária* (ANVISA) (Balbino and Dias, 2010), the Brazilian sanitary vigilance agency, there are four records of severe ADRs to *Bauhinia forficata* ('such as hepatic problems, including cirrhosis and renal pain, reported for a medication commercialized without registration').

Generally speaking, 'patas-de-vaca' are urban trees and therefore can have high levels of contamination by pollution, which favors the occurrence of toxic effects. This is the reason why the City Hall of Diadema cut the tree after users complaints, making it impossible for us to identify exactly which species was used. As a result of those limitations, two other samples of 'pata-de-vaca' were collected in the city of Diadema and identified by technicians of the *Instituto de Botânica de São Paulo* (Botanical Institute of São Paulo), to complement the data of this study. They were identified as *Bauhinia variegata* L. and *B. purpurea* L., but no data of ADRs were found for these species either.

Consequently, although the literature did not corroborate the possible ADR to the preparation ingested, we cannot rule out the possibility that it was an ADR not described yet. Relation of causality: unclassifiable. Severity: moderate. Expectance: unexpected adverse reaction. Seriousness: serious.

Bitter wood ('pau-tenente') (Table 4) regards the wood of the species *Picrasma crenata* Engl. In Engl. & Prantl (Simaroubaceae), characterized by a strong bitter taste and used popularly as a digestive, hypotensive and hypoglycemiant, among other indications. The only pharmacological study we found (Novello *et al*., 2008) points to discreet hypoglycemiant and anti-gastric ulcer effects, as well as low toxicity to rodents (DL50 $>$ 5 g/kg).

The two samples purchased as bitter wood fit the description of the wood of *Picrasma crenata*. Therefore, there is no evident relation between the reports obtained from the patient (Table 4) and the reports in the literature. Additionally, the glycemia increase contradicts the hypoglycemiant results obtained in an animal model (Novello *et al*., 2008) and the popular use mentioned before. Consequently, according to the causality relation of the WHO, the ADR described cannot be associated with the use of that plant. Relation of causality: unrelated. Severity: moderate. Expectance: unexpected adverse reaction. Seriousness: serious.

The product 21-herb tea[1] (Table 5) corresponds to a mixture of 21 different species (mentioned in its label by their vernacular and incomplete botanical names): Avocado (*Persea gratissimo*), artichoke (*Cynara scolymus*), rosemary (*Rosmarinus officialis*), bancha (*Camellia sinensis*), boldo (*Peumus boldus*), 'chá-de-bugre' (*Cordia salicifolia*), green tea (*Camellia sinensis*), "cana-do-brejo" (*Costus spicatus*), citronella (*Melissa officinalis*), 'carqueja' (*Baccharis gaudichaudiana*), horsetail herb (*Equisetum arvense*), 'espinheira-santa' (*Maytenus ilicfolia*), passion flower (*Passiflora alata*), senna (*Cassia angustifolia*), lemon balm (*Cymbopogon citratus*), stevia (*Stevia rebaudiana*), star anise (*Illicum verum*), chamomile (*Matricaria recutita*), blue mallow (*Malva sylvestris*), 'batata-de-purga' (*Operculina macrocarpa*), anise (*Pimpinella ansisum*). Many of these plants are part of the international phytotherapy. According to the advertisement on the Internet, the 21-herb tea is commercialized to help people lose weight.

The interviewee (Table 5) reported she had an allergy after drinking the tea. Even though it is difficult, or almost impossible, to establish a causal relation with one specific component of this mixture, data in the literature regarding the ingredients considered separately mention possible allergies. Species of the Asteraceae family (artichoke, chamomile, 'carqueja' [*Baccharis trimera*]) produce allergic reaction in sensitive individuals due to the presence of sesquiterpene lactones, which might explain the reaction our interviewee reported (Sasseville, 2009). Additionally, the species lemon grass and anise are mentioned in reports of contact dermatitis after its topic use (Gruenwald *et al*., 2000).

Therefore, according to the WHO relation of causality, the case involving the 21-herb tea may be an ADR to the product. Nevertheless, it is not possible to attribute this reaction to one single component of the mixture. Relation of causality: unclassifiable. Severity: mild. Expectance: expected adverse reaction. Seriousness: non-serious.

CONCLUSION

These data reinforce the growing need to actively monitor the use of HPs and other herbal medicines, so that health professional and users might have a better understanding of the possible risks. This would require more adequate methods and tools to control and rationalize the use of these products.

We believe the strategies used in this study enabled us to perform an analysis of the possible ADRs related to the HPs mentioned by the interviewees. Moreover, they point to the need to toxicity studies of Bitter wood, and mainly 'pata-de-vaca', since they are largely used in popular medicine to treat diabetes.

[1]The trade of these HPs is clandestine (not approved by the sanitary vigilance). It is a product very common in Brazil, known as 21-, 30- or 37-herb tea, indicated for weight loss. As a result of its clandestine trade, we were unable to contact the producer in order to request data that could contribute to the analysis.

Additionally, educational actions aimed at users and health professional are called for in order to establish better communication between the general public and professionals in the medical area, as well as to stress the importance of ADRs to HPs to be reported.

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Conflict of Interest

The authors have declared that there is no conflict of interest.

REFERENCES

[ANVISA] Agência Nacional de Vigilância Sanitária. 2008. Instrução Normativa n°5 de 11 de Dezembro de 2008. Determina a publicação da Lista de medicamentos fitoterápicos de registro simplificado. Brasil, Diário Oficial da União, nº242; 56–58.

[PNUD] Programa das Nações Unidas para o Desenvolvimento. 2000. Atlas do Desenvolvimento Humano, Brasília. Available at: http://www.pnud.org.br/atlas/tabelas/index.php, last access: 10 June 2012.

Balbino EE, Dias MF. 2010. Farmacovigilância: um passo em direção ao uso racional de plantas medicinais e fitoterápicos. *Rev Bras Farmacogn* **20**: 992–1000.

Barnes J. 2003. Pharmacovigilance of herbal medicines: a UK perspective. *Drug Saf* **26**: 829–851.

Berlyn GP, Miksche JP. 1976. Botanical microtechnique and cytochemistry. Iowa State College Press: Ames.

Bernard HR. 1988. Research Methods in Cultural Anthropology. Sage Publications: London.

Boulenger J-P, Uhde TW, Wolff EA, Post RM. 1984. Increased Sensitivity to Caffeine in Patients With Panic Disorders: Preliminary Evidence. *Arch Gen Psychiatry* **41**: 1067–1071.

British Pharmacopoeia. 2012. British Pharmacopoeia online, vol. **IV**. Stationery Office: London. Available at: http://bp2012.infostar.com.cn/Bp2012.aspx?a=query&pid=5188, last access: 21 Dec 2012.

da Cunha AM, Menon S, Menon R, Couto AG, Urger CB, Biavatti W. 2010. Hypoglycemic activity of dried extracts of *Bauhinia forficata*. *Phytomedicine* **17**: 37–41.

ESCOP monographs. 2003. Sennae. In The European Scientific Cooperative on Phytotherapy, 2nd ed. Thieme: Exeter, UK.

Freitas A. 2007. Estrutura de mercado do segmento de fitoterápicos no contexto da indústria farmacêutica brasileira. Ministério da Saúde, Brazil: Brasília. Available at: http://portal.saude.gov.br/portal/arquivos/pdf/estudo_fitoterapicos.pdf, last access: 08 June 2011.

Fuentes O, Arancibia-Avila P, Alarcón J. 2004. Hypoglycemic activity of *Bauhinia candicans* in diabetic induced rabbits. *Fitoterapia* **75**: 527–532.

Grobbe DE, Rimm EB, Giovannucci E, Colditz G, Stampfer M, Willet W. 1990. Coffee, caffeine and cardiovascular disease in men. *N Engl J Med* **323**: 1026–1032.

Gruenwald J, Brendler T, Jaenicke C. 2000. PDR for herbal medicines. Medical Economics Company: Montvale, NJ; 465–466.

Hietala P, Marvola M, Parviainen T, Lainonen H. 1987. Laxative potency and acute toxicity of some anthraquinone derivatives, Senna extracts and fractions of Senna extracts. *Pharmacol Toxicol* **61**: 153–156.

Lane JD, Adcock RA, Williams RB, Kuhn CM. 1994. Caffeine effects on cardiovascular and neuroendocrine responses to acute psychosocial stress and their relationship to level of habitual caffeine consumption. *Psychosom Med* **52**: 320–336.

Matsuo Y, Tanaka T, Kouno I. 2006. A new mechanism for oxidation of epigallocatechin and production of benzotropolone pigments. *Tetrahedron* **62**: 4774–4783.

Michael D, Green D, Mical F, Leon G. 2000. Reference Guide on Epidemiology. In Reference Manual on Scientific Evidence (2nd edn). Federal Judicial Center; 333–400. Available at: http://www.fjc.gov/public/pdf.nsf/lookup/sciman00.pdf/$file/sciman00.pdf, last access: 10 June 2012.

Morais SM, Dantas JDP, Silva ARA, Magalhães EF. 2005. Plantas medicinais usadas pelos índios Tapebas do Ceará. *Rev Bras Farmacogn* **15**: 169–177.

Novello CR, Bazotte RB, Bersani-Amado CA, Marques LC, Cortez DGA. 2008. Toxicological and Pharmacological Studies of *Picrasma crenata* (Vell.) Engler (Simaroubaceae) in Mice and Rats. *Lat Am J Pharm* **27**: 345–358.

Rawlins M, Thompson J. 1991. Mechanisms of adverse drug reactions. In Davies D, Textbook of adverse drug reactions (4nd edn). Oxford University Press: Oxford; 18–45.

Roeser KR. 1962. Die Nadel der Schwarzkiefer-Massenprodukt und Kunstwerk der Natur. *Mikrokosmos* **61**: 33–36.

Sass JE. 1951. Botanical microtechnique (2nd edn). Iowa State College Press: Ames.

Sasseville D. 2009. Clinical Patterns of Phytodermatitis. *Dermatol Clin* **27**: 299–308.

Sharangi AB. 2009. Medicinal and therapeutic potentialities of tea (*Camellia sinensis* L.) – A review. *Food Res Int* **42**: 529–535.

Soares JAR, Galduróz JCF, Rodrigues E. 2010. Rede de Comércio das Drogas Psicoativas na Cidade de Diadema e o seu interesse para a Saúde Pública. *Saude Soc* **19**: 310–319.

Souza RAG, Sichieri R. 2005. Consumo de cafeína e de alimentos - fonte de cafeína e prematuridade: um estudo caso – controle. *Cad Saude Publica* **21**: 1919–1928.

United States Food and Drug Administration. 1985. 21 CFR Part 334: Laxative products for over-the-counter human use; tentative final monograph. *Fed Regist* **50**(10): 2124–2158. Available at: http://goo.gl/dNE9n

Veiga VF Jr. 2008. Estudo do consumo de plantas medicinais na Região Centro-Norte do Estado do Rio de Janeiro: aceitação pelos profissionais de saúde e modo de uso pela população. *Rev Bras Farmacogn* **18**: 308–313.

Wong A, Castro EGR. 2003. Aspectos toxicológicos dos fitoterápicos. *Arq Bras Fitomed Cient* **1**: 96–102.

World Health Organization. 2000. Safety Monitoring of Medicinal Products: Guidelines for setting up and running a Pharmacovigilance Centre. The Uppsala Monitoring Centre. Available at: http://who-umc.org/graphics/24747.pdf, last access: 11 Dec 2012.

World Health Organization. 2002. The Importance of Pharmacovigilance: Safety Monitoring of medicinal products. The Uppsala Monitoring Centre: Geneva.

World Health Organization. 2012a. The use of the WHO-UMC system for standardized case causality assessment. The Uppsala Monitoring Centre. Available at: http://who-umc.org/Graphics/24734.pdf, last access: 20 Dec 2012.

World Health Organization. 2012b. Glossary of terms used in Pharmacovigilance. Uppsala Monitoring Centre. Available at: http://who-umc.org/Graphics/24729.pdf, last access: 11 Dec 2012.

Yang XR, Ye CX, Xu JK, Jiang YM. 2007. Simultaneous analysis of purine alkaloids and catechins in *Camellia sinensis*, *Camellia ptilophylla* and *Camellia assamica* var. kucha by HPLC. *Food Chem* **100**: 1132–1136.

