

# DEVELOPMENT OF INSTRUMENT TO REPORT AND ASSESS CAUSALITY OF ADVERSE EVENTS RELATED TO HERBAL MEDICINES

## DESARROLLO DE UN INSTRUMENTO PARA REPORTAR Y EVALUAR LA CAUSALIDAD DE LOS EVENTOS ADVERSOS ASOCIADOS A PLANTAS MEDICINALES

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### ABSTRACT

**Background:** The use of herbal medicines is justified empirically using ethnopharmacological knowledge, which has limitations. Reports of adverse events (AE) may contribute for safety, quality, and effectiveness assessment. **Objectives:** This study aimed to develop an instrument to allow detection and evaluation of the causal likelihood of AE related to herbal medicines. **Methods:** A quantitative methodological development research intervention was performed with primary care health professionals. Two cases were distributed in an interval of one week in order to allow for completion of the proposal form. The within-rater reliability was calculated and classified into satisfactory, regular, and unsatisfactory, according to essential, necessary, and recommended items reported. **Results:** Fifty-seven professionals were enrolled. A high degree of the within-rater reliability was observed for the most essential, necessary, and recommended fields. The instrument contributed to assessment of definite causal association, once the duration of reactions including evolution, withdrawal, and reposition items showed high reliability. Most fields poor and weak filled were related to quality defects, such as popular name and appearance. **Conclusions:** Data suggest the instrument is adequate to report AE arising from herbal medicines. Owing to information regarding to organoleptic characteristics, the instrument is different from drug instruments. Therefore, it is intended to improve AE reports related to herbal medicines and contribute for appropriate use.

**Keywords:** Herbal medicine; adverse drug reaction reporting systems; pharmacovigilance; risk assessment; product Surveillance; postmarketing.

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## RESUMEN

**Antecedentes:** Hierbas medicinales son utilizadas empíricamente con la base en el conocimiento etnofarmacobotánico, los cuales tienen limitaciones. Los informes de los eventos adversos (EA) pueden contribuir a la seguridad, la calidad y la evaluación de la eficacia de estos productos. **Objetivos:** El objetivo del estudio fue desarrollar un formulario para permitir la detección y evaluación de la probabilidad causal de EA relacionado al uso de plantas medicinales e fitoterápicos. **Métodos:** Investigación cuantitativa, de desenvolvimiento se llevó a cabo con los profesionales sanitarios de atención primaria. Dos casos fueron distribuidos, en un intervalo de una semana, con el fin de ser llenado en el formulario propuesto. La fiabilidad inter-observadores del instrumento fue evaluada y los resultados fueron clasificados en satisfactorio, regular e insatisfactorio, según los datos esenciales, necesarios y recomendados que fueran rellenos en el formulario de notificación. **Resultados:** Cincuenta y siete profesionales fueron elegibles. Se observó alto grado de fiabilidad entre observadores para la mayoría de los campos esenciales, necesarios y recomendados. El formulario contribuyó para la evaluación de la asociación causal definitiva, una vez que los campos de duración de las reacciones; evolución, retirada y re-exposición tuvieron alta fiabilidad. La mayoría de los campos flacamente llenados estaban relacionados con defectos de calidad, tales como: nombre popular y apariencia. **Conclusiones:** Los datos sugieren que el formulario propuesto es adecuado para reportar EA derivados de hierbas medicinales. Por la información relativa a las características organolépticas, el instrumento es diferente de lo instrumento para notificación de medicamentos. Por lo tanto, se pretende mejorar los informes de EA relacionados con los productos naturales y contribuir para el uso apropiado.

**Palabras clave:** Medicina de hierbas; sistemas de registro de reacción adversa a medicamentos; farmacovigilancia; medición de riesgo; vigilancia de productos comercializados.

## INTRODUCTION

According to the World Health Organization (WHO)<sup>[1]</sup>, traditional medicine is an important instrument for pharmaceutical assistance, since approximately 70-90% of the world population uses herbal medicines as the only manner to access basic healthcare<sup>[1,2]</sup> for both the prevention and control of diseases<sup>[3]</sup>.

In Brazil, 82% of citizens have consumed these kind of products<sup>[4]</sup> for treatment of minor disorders and chronic illness<sup>[5]</sup>. In general, ethnobotanical knowledge underlies indication, dosage, and mode of administration of herbal medicines<sup>[6]</sup>. However, according to Rodrigues and Barnes<sup>[7]</sup>, this traditional framework is limited in the detection of adverse reactions, contraindications, toxicity, and other important aspects to establish the safety profile of natural substances.

Herbal medicines are associated with the development of serious adverse reactions<sup>[8-10]</sup>, which may cause life-threatening<sup>[9]</sup>, hospital admissions<sup>[11]</sup>, and death<sup>[8,9,12]</sup>. In addition, other factors may increase the risk of occurrence of adverse events, such as tampering, poor quality, lack of proper

identification, contamination and inappropriate use<sup>[13]</sup> as well as improper storage and handling<sup>[14]</sup> and packaging<sup>[15]</sup>.

However, there is an underestimation of causal association between adverse effects and the use of herbal medicines, since users do not inform health professionals about their administration<sup>[2,14,16]</sup>, and since they are not able to correlate unwanted clinical manifestation with intake<sup>[17]</sup>. Besides, the lack of awareness among professionals in requesting information about the consumption of herbal medicines during pharmacological anamnesis as well as the absence of a specific form to reporting adverse events related to medicinal plants and phytotherapy<sup>[18]</sup> also hinder safety surveillance.

Therefore, more effective methods for recognition of negative clinical outcomes associated with use of herbal medicines are needed to strengthen actions of phytosurveillance in Brazil. In this setting, the present study aimed to perform the following: i) develop an instrument to report adverse events related to herbal medicines and ii) verify its ability to perform causality assessment and improve risk communication.

## MATERIAL AND METHODS

### Study population and design

A quantitative methodological development research was carried out with health professionals who practiced in the northwest region of São Paulo State from March 2011 to March 2012 in order to develop an instrument to report problems of safety, therapeutic failure, and quality deviations of herbal medicines.

All primary healthcare professionals (physicians, pharmacists, nurses, dentists, and nutritionists) who agreed to participate in the study and signed an informed consent form were enrolled. Exclusion criteria comprised professionals who, after three attempts, did not respond to the invitation to participate in the study as well as those who returned unfilled forms in the second phase of the research. Therefore, it is an intentional sample applied to instruments developed to be pre-tested<sup>[19]</sup>.

### Instrument development (form)

#### *Generation of the initial sample of items*

The form to report adverse events related to the use of herbal medicines was designed according to WHO guidelines<sup>[20]</sup>, which advocate the presence of several items to allow quality information, such as the following: 1) identification of patient (initials, demographic characteristics, medical history, and risk factors); 2) the suspected product (species, Latin and popular names, part used, method of preparation, manufacture, country of origin, batch, supplier, and validity); 3) mode of administration (dose and route); 4) indication and reason for use; 5) adverse event (clinical evolution, laboratory tests, onset and end of the event, seriousness, data of withdrawn, and rechallenge); 6) concomitant medications (prescription drugs and self-medication); and 7) demographic data of the reporter.

The instrument was designed in a semi-structured way with an essay and multiple choice questions<sup>[21]</sup> in order to enable identification of problems related to safety, quality, and effectiveness of herbal medicines (Figure 1). It can be accessed here: <http://www2.fcfar.unesp.br/Home/Alunos/naf/formulario-de-notificacao-de-reacoes-adversas-afitoterapicos-e-plantas-mediciniais.pdf>.

#### *Qualitative assessment of the items*

Qualitative assessment of technical terms applied to the development of the form. The items of the instrument were evaluated by two PhD docents of School of Pharmaceutical Sciences of Unesp. All fields were considered applicable for the population of the study. There was not the need to reformulate any items.

### Data collection

Assessment of appropriateness of the instrument to report adverse events was performed in three phases.

During the first phase a pilot study was conducted with undergraduate students taking a pharmacy course at the School of Pharmaceutical Sciences in Unesp. A clinical case (case 1) of adverse reaction with likelihood of excellence (probability of occurrence classified as definite) was developed and distributed among volunteers.

Case 1 described a married woman (45 years old) who reported the use of eucalyptus leaves to treat nasal congestion. According to the patient, the leaves were collected in a field near her house. When she felt nasal congestion, she boiled an unmeasured quantity of leaves with water. The vapor produced was inhaled. After three weeks of treatment, she experienced abdominal pain, diarrhea, and moments of delirium. She also noted cyanosis in her extremities. After clinical assessment by a physician, she was informed to discontinue the use of the plant. Concomitant pharmacotherapy included acetylsalicylic acid 500mg once a day and captopril 25mg three times per day. A few weeks after discontinuing the herbal medicine, the patient recovered.

Moreover, samples of suspected plant were sent to undergraduate students in order to analyze them and complete the instrument.

The second and third phases of the study were performed according to the methodology developed by Naranjo et al. (1981)<sup>[22]</sup>. Therefore, a test-retest was carried out.

The second phase comprised the distribution of Case 1 for primary care health professionals as well as the samples of the suspect plant. Subjects should analyze the case and the samples to report them in the instrument.

A week later (third phase), a new clinical case (Case 2) was made available for health professio-

nals. Case 2 described a single woman (50 years old) who reported feeling stress and insomnia. Her neighbor recommended Kava-kava to treat her anxiety and sleep difficulties. She prepared tea with leaves during several months or cooked the roots with coconut milk. She bought the plant from an herbalist. After three months, the patient noticed the occurrence of a cutaneous rash, red eyes, and yellow nails and fingers. She ingests alcoholic beverages during the weekends and has clinical history of hepatitis. To recover from hangovers, she uses acetaminophen (750 mg). Her physician recommended discontinuation of the plant, and after ten days, she completely recovered.

Herbal samples were also distributed among volunteers in the third phase. They analyzed the material and filled out the instrument. Herbal samples provided were not necessarily responsible for the occurrence of the observed event. We opted for this strategy to assess whether the volunteers would perform the analysis of the material, allowing their identification.

Clinical cases were elaborated based on scientific articles<sup>[23-26]</sup> available in the databases PubMed and Lilacs. Since each case had its own specified age and sex of patients as well as the reason and mode of use of herbal medicines, clinical history, and polypharmacy, several gold standard answers were adopted: satisfactory fulfillment of essential, necessary, and recommended fields regarding information related to identification of patients and plants; drugs used concomitantly and clinical history; and data of the reporter.

### Data Analysis

Content analysis of the instrument with both clinical cases was performed, comparing the items filled by health professionals with a gold-standard<sup>[1]</sup>. OPS (2011)<sup>[1]</sup> classified the information to be reported according to the degree of relevance: essential, necessary and recommended.

Then, content analysis considered the fill of the correspondent items in the form, according to all adverse events identified in clinical cases and relevance of information, as proposal by OPS. The agreement of volunteers to complete the information in the fields considered essential, necessary, and recommended to be reported was demonstrated using coefficient kappa.

Essential items are those which allow identifying the suspicious plant, the adverse event, and the

patient. The completion of these fields enables the analysis of causality, since it promotes assessment of temporal association (development of adverse event and the intake of the drug); pharmacological plausibility (if the mechanism of action of the active principle may explain the occurrence of the adverse event); the exclusion of alternative causes (other situations that could explain the development of the observed event, such as drug interactions, concomitant drugs, clinical condition of the patient, among others); and verifying that the event has been described for the plant used.

Necessary items complement causality analysis and allow the assessment of the clinical course of the adverse events (outcomes, seriousness, dechallenge, and rechallenge). The lack of necessary information in the form does not hinder causality assessment, since follow up makes the collection of missing data possible in order to complete the evaluation.

Recommended items collaborate with classification of adverse events in adverse reaction, quality deviations, therapeutic failure, or medication errors.

Accuracy and integrity of reports were analyzed according to the proportions of the within-rater reliability in completing the items classified as essential, necessary, and recommended to be reported. Thus, the kappa coefficient was calculated. It was stipulated that 90 %, 80 %, and 50 % of the essential, recommended, and necessary items should be filled, respectively. Week agreement was observed when  $0.21 < k < 0.40$ , moderate agreement was observed when  $0.41 < k < 0.60$ , good agreement was observed when  $0.61 < k < 0.80$  and very good agreement was observed when  $0.81 < k < 1.0$ .

### Approval by Ethics Committee Research:

The study (protocol CEP/FCF/CAR n° 08/2009) was approved by the Ethics Committee in Research at the School of Pharmaceutical Sciences of Unesp.

## RESULTS

The pilot study was carried out with 20 students. Most volunteers (n=18) filled the adverse events identified in the correspondent item in form correctly. These findings show the terminology used to develop the instrument is adequate to report adverse reactions and quality deviations. However, due to lack of data regarding medication errors and therapeutic failure in the reports, these items were included to contribute with reporting of any kind of problems related to herbal medicines.

A hundred and seven health professionals were invited to participate of phase 2, of which 57 (53.3%) returned both forms completed (48 pharmacists; five nutritionists; two nurses; a physician; and a dentist). According to demographic characteristics, most volunteers were women (n=49) and non-elderly people (mean 30.5 years old; minimum 21 and maximum 60 years old).

Data show that 12 out of 21 fields of instrument had moderate (n=7) and very good agreement (n=5): nine of them were essential, two were necessary, and one was recommended, respectively (Table 1).

In general, the proposed instrument was able to identify adverse reaction, quality deviation, and medication errors, since among the 14 essential fields (Table 1), 12 of them showed a high degree of within-rater reliability ( $k > 0.61$ ) (Table 2). Five items contribute for identification of adverse reaction; five promote identification of quality deviation; and the other three provide recognition of medication errors.

Among five necessary fields (Table 1), two (Table 2) showed moderate within-rater reliability ( $0.41 \leq k \leq 0.61$ ), which was related to the identification of quality deviations. Considering the two fields recommended to be filled in the form (Table 1), one was related to medication errors (Table 2), which had poor agreement ( $k < 0.41$ ).

Items associated with causality assessment that enable definitive adverse reaction imputations (duration, description, evolution of reaction, and dechallenge and rechallenge of plant) showed a high degree of within-rater reliability ( $k > 0.61$ ) in both clinical cases (Table 2).

## DISCUSSION

Signal generation in pharmacovigilance depends on the quantity and quality of adverse drug reports submitted to sanitary agencies<sup>[27]</sup>. In Brazil, after development of electronic reporting of adverse events (NOTIVISA), in 2008, no reports of problems related to the use of herbal medicines was received by the National Surveillance Agency (ANVISA)<sup>[8]</sup>. Our findings suggest the form developed is an appropriate instrument to report adverse events arising from herbal medicines.

In Africa, although herbal medicine pharmacovigilance programs covered suspected adverse reactions in 14 (87.5%) countries, medication errors

in 5 (31.2%) countries, falsification and adulteration in 2 (each 12.5%) countries, and drug interactions in 1 (6.3%) country, particular attention to the development of surveillance of natural products is required<sup>[28]</sup>.

Underreporting<sup>[18]</sup> and poor quality of information hinders causality association<sup>[29,30]</sup>. Therefore, specific tools are needed to contribute for analysis of safety, quality, and effectiveness of these products<sup>[18]</sup>.

The proposed instrument met this need, since it was effective in detecting adverse events related to herbal medicines. According to Barnes (2003)<sup>[18]</sup>, a specific instrument appropriately designed to report and to assess the causality of adverse events arising from herbal medicines may be a strategy to decrease underreporting in phytosurveillance.

Furthermore, the instrument contributed for recognition of adverse reactions with high likelihood (definite and probable). Maximum degree of imputation depends on dechallenge and rechallenge of natural substance with recurrent of undesired effects<sup>[31]</sup>. These fields, as well as those related to "description" and "evolution of reaction", were satisfactorily filled in both cases reported by health professionals. Therefore, there is evidence that our form contributes for the improvement of the quality of information reported, which is essential to causality assessment of adverse reaction.

Recovery field is not considered an essential item, since reports *per se* do not allow follow up of each case<sup>[32]</sup>, clinical outcomes are unknown during the detection of a suspicion of adverse event. Therefore, although this field has been poorly filled, this is not a limitation of the proposed instrument, since the outcomes arising from adverse events may be collected during the follow up of the cases.

The improvement of quality of information by proposed form also contributed to the detection of medication errors, mainly, prescription and administration. For example, cases of administration errors can be minimized by filling in fields "part of the plant used"; this enables verification whether the correct part of herbal medicine was used and "mode of use" favors the analysis of suitable extraction method and dosing schedule.

The fields of "polypharmacy"; "onset of concomitant drugs", and "suspension of use" allows identifying prescriptions errors, such as indication and drug interactions. Skalli et al. (2012)<sup>[33]</sup> stated that reports of drug interactions involving herbal

medicines and allopathic drugs are very important to delineate the safety profile of these products. The poor concordance obtained in the field “relevant data” (where volunteers would inform morbidity and co-morbidity, drug allergies, and liver or kidney failure) make the analysis of therapeutic failure and toxicity difficult, since they may be developed by multifactorial conditions, such as genetic polymorphisms, low dose, overdose, tolerance, quality deviations, adulterations, among others. Correctly completing this field should improve the recognition of the contribution of the plant in the development of adverse event.

Low within-rater reliability might be explained considering that, in the first case, there was no clinical relevant information worthy of note, since the patient was healthy. However, it was expected that professionals could signal the absence of alternative causes that could contribute to the occurrence of the medication errors verified.

Finally, the instrument identifies quality deviations in a regularly way, especially regarding to tampering and contaminating herbal medicine samples. This finding can be justified based on the subjectivity associated to items “smell”, “color”, “appearance”, and “texture”. However, satisfactory filled fields “scientific name” may minimize bias related to description of organoleptic characteristics provided by health professionals, since it is possible to compare it with a description provided by official literature; however, this may increase quality deviations<sup>[15,34]</sup>. Moreover, the scientific name of herbal medicine is important for the standardization and harmonization of terminology within an international framework<sup>[17]</sup> in order to increase the effectiveness of post-marketing in regulation and supervision of natural products available in the market.

To improve the documentation of adverse event reports, mainly of quality deviations, the development of educational interventions for health professionals is recommended. These methods have proven effective to increase knowledge, attitudes, and skills regarding the spontaneous reporting of adverse drug events<sup>[35,36]</sup>. Therefore, we suggest adaptation of the approach and their content for monitoring of herbal medicines in order to fundamentally standardize the analysis of the organoleptic parameters of the products and to highlight the importance to notify problems of safety, quality, and effectiveness related to the use of natural substances.

The awareness of health professionals and users of herbal medicines began in 2007, when the Brazilian Information Center on Psychotropic Drugs (Cebrid) launched the newsletter called PANFLAVI, which is release three times each year<sup>[37]</sup>.

A pharmacovigilance system of herbal medicines also started in the same year by the publication of a notification form of adverse reactions related to herbal medicines (RAMP) by the institution. Therefore, the instrument form developed in this study will allow identification of other potential adverse events associated with the use of these products, such as handling and packaging<sup>[14,15]</sup>, improper storage and identification<sup>[15]</sup>, serious adverse reactions<sup>[38]</sup>, and medication errors<sup>[13]</sup>.

This instrument is suitable for identification of adverse events related to herbal medicines, since it improves upon the previously available forms by ANVISA and CEBRID and expands the possibility of identification of events other than adverse reaction. The present form differs from reports of allopathic drugs, since it provides fields regarding organoleptic characteristics (smell, color, texture, appearance) and mode of use. Thus, it is intended to improve adverse event reporting related to herbal medicines and to contribute for appropriate use by expanding the usage information.

Limitations of the study:

Our findings should be interpreted with caution, because of the following limitations. Due to clinical cases, this study only included adverse reactions to herbal medicines; sessions relating to phytotherapies have not been assessed. Also, the form does not meet the criteria for notification of ready mixes of herbal medicines due to the difficulty of identifying the components of formulations. Furthermore, we use a non-probabilistic sample due to the lack of access of a complete list of health professionals in the region of the study. Then, findings should not be generalized.

## CONCLUSIONS

The instrument developed in this study is suitable for identification of adverse events related to herbal medicines. Thus, it contributes to risk communication in phytosurveillance, since it allows voluntary reporting and causality assessment of the events identified. The instrument is also able to satisfactorily identify safety issues with a high degree of imputation (definitive) and quality deviations

problems. The present form differs from reports of allopathic drugs, since it provides fields regarding organoleptic characteristics (smell, color, texture, appearance) and mode of use. Thus, it is intended to improve adverse event reporting related to herbal medicines and to contribute for appropriate use by including usage information.

## CONFLICT OF INTEREST

The authors do not have any kind of conflict of interest.

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## AUTHORS' CONTRIBUTIONS

Patricia de Carvalho Mastroianni and Luis Vitor da Silva Sacramento contributed to conceptualization, methodology, supervision, validation and writing (review and editing). Marília Amaral Costa and Fabiana Rossi Varallo contributed to data collection, analysis, validation, visualization and writing (original draft preparation).

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**Table 1:** Classification of form's fields according to degree of relevance and indication of reporting.

	ESSENTIAL	NECESSARY	RECOMENDED
ADVERSE REACTION (AR)	Duration of AR Description of AR Clinical evolution of AR Dechallenge of herbal medicine Rechallenge of herbal medicine	Procedure Patient recovery	
QUALITY DEVIATIONS (QD)	Popular name of plant Scientific name of plant Part of used of plant Description of part used Color Appearance	Description of plant Smell	Texture
MEDICATION ERRORS (EM)	Part of used of plant Posology Color Polypharmacy Onset of use	Smell Description of plant Withdraw of concomitantly drugs	Relevant data about patient
THERAPEUTIC FAILURE (TF)	Drugs used Onset of treatment End of treatment Drug ineffectiveness		



**Table 2.** Within-raters reliability of adverse reaction reporting carried out with the aid of developed form, according to items considered essential, necessary and recommended to be filled.

ADVERSE EVENT	ESSENTIAL				NECESSARY				RECOMMENDED			
	Fields	Case 1 N (%)	Case 2 N (%)	Kappa±SD (CI)	Fields	Case 1 N (%)	Case 2 N (%)	Kappa±SD (CI)	Fields	Case 1 N (%)	Case 2 N (%)	Kappa±SD (CI)
ADVERSE REACTION	Duration of AR	51 (89.5)	52 (91.2)	0.90±0.07* (0.75-1.00)	Procedure	29 (50.9)	31 (54.4)	0.93±0.04* (0.86-1.00)				
	Description of AR	53 (92.9)	55 (96.5)	0.65±0.18* (0.30-1.00)	Recovery	56 (98.2)	57 (100.0)	Zero ±0.75 (0.00-1.00)				
	Evolution	30 (52.6)	34 (59.6)	0.86±0.05* (0.75-0.96)								
	Dechallenge	55 (96.5)	53 (92.9)	0.65±0.18* (0.30-1.00)								
	Rechallenge	24 (42.1)	30 (52.6)	0.79±0.06* (0.67-0.91)								
QUALITY DEVIATION	Popular name	51 (89.5)	57 (100.0)	Zero±0.30 (0.00-0.6)	Description of plant	18 (31.6)	33 (57.9)	0.50±0.08 (0.04-0.67)	Texture	36 (63.2)	27 (47.4)	0.70±0.07* (0.55-0.83)
	Scientific name	22 (38.6)	29 (50.9)	0.75±0.06* (0.63-0.89)	Smell	52 (91.2)	42 (73.7)	0.42 ±0.12 (0.18-0.67)				
	Part of plant used	55 (96.5)	54 (94.7)	0.80±0.15* (0.49-1.00)								
	Part of plant to describe	54 (94.7)	54 (94.7)	1.00* (1.00)								
	Color	44 (77.2)	31 (54.4)	0.52±0.08 (0.35-0.70)								
MEDICATION ERRORS	Appearance	42 (73.7)	54 (94.7)	0.27 ±0.14 (0.00-0.55)								
	Posology	20 (35.1)	35 (61.4)	0.51±0.08 (0.35-0.67)	Drug withdrawal	33 (57.9)	33 (57.9)	1.00* (1.00)	Other data	5 (8.8)	28 (49.1)	0.18±0.10 (0.00-0.38)
	Polypharmacy	39 (68.4)	25 (43.9)	0.53±0.08 (0.37-0.70)								
	Onset of polypharmacy	39 (68.4)	25 (43.9)	0.65±0.18* (0.30-1.00)								

Note: AR = adverse reaction; \* Satisfactory fill; % of concordance in each case.

**Formulário de Notificação de Reações Adversas a Fitoterápicos e Plantas Medicinais**

Se há suspeita que alguma reação adversa pode estar relacionada a um Fitoterápico ou a uma Planta Medicinal, por favor preencha este formulário.

**Informações sobre o paciente**

Iniciais do Paciente: \_\_\_\_\_ Idade: \_\_\_\_\_  
 Peso (se conhecido): \_\_\_\_\_ Sexo: Masculino [ ] Feminino [ ]

**Informações sobre a Reação Adversa suspeita**

Data da Reação Adversa: \_\_/\_\_/\_\_\_\_  
 Duração da Reação adversa: [ ] Imediata [ ] Minutos [ ] Horas [ ] Dias  
 Descreva a reação adversa (sinais e sintomas):  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

[ ] Necessitou de internação  
 [ ] Alterou-se a posologia  
 [ ] Continuou com a medicação  
 [ ] Houve um tratamento específico:  
 \_\_\_\_\_

**Evolução da reação:**  
 [ ] Ainda não recuperado [ ] Risco de Morte [ ] Anomalia Congênita [ ]  
 Carcinogênico [ ] Desconhecida

**Recuperação do paciente:**  
 [ ] Ocorreu [ ] Ocorreu, mas com seqüela [ ] Não ocorreu

**Retirada da Medicação:**  
 [ ] Houve melhora [ ] Não houve melhora [ ] Desconhecido

[ ] Verde claro [ ] Amarelado [ ] Tons de marrom ou castanho [ ] Outra  
 • **Para Flor:**  
 [ ] Amarela [ ] Vermelha [ ] Roxa [ ] Laranja [ ] Bordô [ ] Azul [ ] Branca [ ] Rosa [ ] Outra  
 • **Para Fruto/Semente**  
 [ ] Verde [ ] Amarelada [ ] Roxa [ ] Alaranjada [ ] Marrom [ ] Outra

**Aparência:**  
 [ ] Ótima [ ] Boa [ ] Ruim [ ] Embolorada  
**Observações:**  
 \_\_\_\_\_  
 \_\_\_\_\_

**Identificação do Fitoterápico Utilizado**

Nome Comercial: \_\_\_\_\_  
 Princípio Ativo: \_\_\_\_\_  
 Posologia (Concentração, via de administração, frequência e tempo de uso)  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

**Forma Farmacêutica:**  
 [ ] Comprimido [ ] Cápsula [ ] Pomada [ ] Tintura [ ] Geléia [ ] Óleo [ ] Solução  
 [ ] In Natura [ ] Gel [ ] Creme [ ] Supositório  
**Laboratório ou Farmácia de Manipulação:** \_\_\_\_\_  
**Número do lote** \_\_\_\_\_  
**Número de Registro:** \_\_\_\_\_

**Reexposição ao Fitoterápico ou a Planta Medicinal:**  
 [ ] Recorrência da reação [ ] Sem Recorrência [ ] Reintrodução não efetuada [ ] Desconhecido

**Identificação da Planta Medicinal Utilizada**

Nome Popular (Nome vulgar): \_\_\_\_\_  
 Nome Científico: \_\_\_\_\_  
 Parte utilizada da planta: \_\_\_\_\_  
 Como a planta foi utilizada (Posologia, descreva o modo de preparo, a frequência e o tempo de uso).  
 \_\_\_\_\_  
 \_\_\_\_\_

**Descrição breve da planta:**  
 \_\_\_\_\_  
 \_\_\_\_\_

**Descrição complementar:**  
 Escolha qual parte da planta irá descrever:  
 [ ] Folhas [ ] Caule/Casca [ ] Raiz/Casca [ ] Flor [ ] Fruto/Semente

**Textura:**  
 [ ] Lisa [ ] Aveludada [ ] Rugosa [ ] Com espinhos [ ] Áspera

**Odor:**  
 [ ] Agradável [ ] Desagradável [ ] Comum [ ] Ausente

**Cor:**  
 • **Para folhas:**  
 [ ] Verde intenso [ ] Verde claro [ ] Amarelado [ ] Marrom [ ] Outra  
 • **Para Caule/Casca:**  
 [ ] Verde intenso [ ] Verde claro [ ] Amarelado [ ] Outra  
 • **Para Raiz/Casca:**

**Medicamentos Concomitantes e Histórico Clínico**

Medicamento	Princípio Ativo	Posologia	Data
Outros dados relevantes (outros diagnósticos, gravidez, alergias, etc)			

Os medicamentos foram suspensos? [ ] sim [ ] não  
 Data da última ingestão dos medicamentos: \_\_/\_\_/\_\_\_\_

**SIT (Suspeita de Inefetividade Terapêutica)**  
 - Medicamentos utilizados concomitantemente (alopáticos ou fitoterápicos)

Medicamento	Posologia	Lote	Prazo de Validade
Início do Tratamento: __/__/____			
Término do Tratamento: __/__/____			
Inefetividade: Parcial [ ] Total [ ]			

**Dados do Notificador**

Nome: \_\_\_\_\_  
 Categoria Profissional:  
 [ ] Médico [ ] Enfermeiro [ ] Farmacêutico [ ] Dentista [ ] Outro \_\_\_\_\_  
 Número de inscrição no conselho: \_\_\_\_\_ UF: \_\_\_\_  
 E-mail: \_\_\_\_\_  
 Telefone: \_\_\_\_\_

**Figure 1.** Instrument developed to report and promote causality assessment of adverse events arising from herbal medicines.

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