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CURRENT OPINION

Pharmacovigilance of Herbal Medicines

The Potential Contributions of Ethnobotanical and Ethnopharmacological Studies

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Abstract Typically, ethnobotanical/ethnopharmacological (EB/EP) surveys are used to describe uses, doses/dosages, sources and methods of preparation of traditional herbal medicines; their application to date in examining the adverse effects, contraindications and other safety aspects of these preparations is limited. From a pharmacovigilance perspective, numerous challenges exist in applying its existing methods to studying the safety profile of herbal medicines, particularly where used by indigenous cultures. This paper aims to contribute to the methodological aspects of EB/EP field work, and to extend the reach of pharmacovigilance, by proposing a tool comprising a list of questions that could be applied during interview and observational studies. The questions focus on the collection of information on the safety profile of traditional herbal medicines as it is embedded in traditional knowledge, as well as on identifying personal experiences (spontaneous reports) of adverse or undesirable effects associated with the use of traditional herbal medicines. Questions on the precise composition of traditional prescriptions or 'recipes', their preparation, storage, administration and dosing are also included. Strengths and limitations of the tool are discussed. From this interweaving of EB/EP and pharmacovigilance arises a concept of ethnopharmacovigilance for traditional herbal medicines: the scope of EB/EP is extended to include exploration of the potential harmful effects of medicinal plants, and the incorporation of pharmacovigilance questions into EB/EP studies provides a new opportunity for collection of 'general' traditional knowledge on the safety of traditional herbal medicines and, importantly, a conduit for collection of spontaneous reports of suspected adverse effects. Whether the proposed tool can yield data sufficiently rich and of an appropriate quality for application of EB/EP (e.g. data verification and quantitative analysis tools) and pharmacovigilance techniques (e.g. causality assessment and data mining) requires field testing.

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1 Introduction

Pharmacovigilance is not limited to pharmaceutical medicines but also concerns herbal and other traditional medicines. Pharmacovigilance practices and tools though have developed in the context of conventional medicine and have rarely considered the complexities of monitoring the safety of medicines sourced from plants [1]. However, in recent years, several issues have led to a greater awareness of the need to monitor the safety of herbal medicines and deepen understanding of their possible harms (and potential benefits). These issues include the increasing use of herbal medicines in developed countries, greater awareness and acknowledgement that many people living in developing nations are dependent on plants as a major (in some cases, the only) source of medicines, the lack of or weak regulation of these preparations in most countries and the occurrence of high-profile safety concerns associated with the use of herbal medicines.

At international level, the WHO has published guidelines on pharmacovigilance of herbal medicines that include practical advice on how some of the many challenges can be approached [2]. In 2001, the WHO Uppsala

Monitoring Centre (WHO-UMC) introduced a traditional medicines surveillance scheme to stimulate reporting and improve the quality of reports of suspected adverse drug reactions (ADRs) associated with herbal and other traditional medicines. By October 2012, the WHO-UMC database contained over 7.5 million reports [3], of which at least 34,000 related to suspected ADRs associated solely with herbal medicines, and a further (almost) 19,000 for which both herbal and non-herbal substances are implicated, according to the UMC (http://www.who-umc.org).

It is widely accepted that a substantial proportion of the world's population, particularly in developing countries, relies on herbal and other traditional medicines as the primary source of healthcare [4], yet a substantial majority of the herbal ADR reports in the WHO-UMC database originates from developed countries [5]. This may reflect that many developing countries have only participated in the scheme for a short time (e.g. fewer than 10 years). Alternative explanations are that users of herbal medicines in developing countries rarely experience ADRs (which, if true, raises the question 'why?'), or that such ADRs occur but are undetected and/or unreported. In Brazil, as in many other countries, medicinal herbs are traditionally considered to be "natural and therefore free of risks" [6] and this may, in part, explain why few adverse effects are reported.

Ethnobotanical/ethnopharmacological (EB/EP) studies provide a means of examining these issues as well as of collecting data on experiences of ADRs associated with use of specific traditional herbal medicines in order to inform our understanding of their safety profile, including in different populations.

Ethnobotany is the study of the relationships between indigenous people and plants, including how plants are used (e.g. as medicines, as food, in rituals), perceived and managed [7, 8]. Ethnopharmacology can be defined as the "interdisciplinary scientific exploration of biologically active agents traditionally employed or observed by man" [9]. EB studies typically use qualitative (e.g. participant observation, interviews) and/or quantitative (e.g. structured questionnaires) anthropological field techniques to explore traditional botanical knowledge. Ethnopharmacology also utilizes those fieldwork techniques to rescue and document the indigenous medicines, an important cultural heritage before it is lost, and employ phytochemical and other laboratory techniques to explore the scientific basis of the effects of these medicines [10], which comprises plants, animals, fungi and other substances. EB/EP studies have been used extensively to describe uses, doses and dosages, and sources and methods of preparation of traditional herbal medicines [11], but their application to date in examining adverse effects, responses to adverse effects (e.g. use of other herbal preparations, use of antidotes following poisoning), contraindications, toxicity and other aspects relevant to safety is limited.

Against this background, this article aims to contribute to methodologic aspects of EB/EP fieldwork by discussing the potential application of these methods for pharmacovigilance purposes. Specifically, an investigational tool is proposed containing a list of items against which data could be collected and recorded during EB/EP observation and interview studies, such that EB/EP surveys potentially may serve as an additional data resource for use in pharmacovigilance of plant medicines. In addition, the paper explains and elaborates upon the items proposed, and introduces the concept of ethno(phyto)pharmacovigilance – a meeting of ethnobotany/ethnopharmacology and pharmacovigilance – and discusses how these disciplines can contribute to each other. Some of the observations made in this article, especially those on the use of indigenous medicines, are based on the authors' experience and discussions with colleagues over several years.

2 Explanation and Elaboration of the Tool

In Fig. 1, a list of items is proposed for use in EB/EP surveys for collection of data concerning adverse effects associated with herbal medicines. The tool makes reference only to plant medicines contained within traditional prescriptions since they are utilized most commonly in healthcare in this context. Many of the items proposed in the tool are illustrated with examples of data collected from previous EB/EP studies; most examples given originate from EP surveys developed by one of the authors (Eliana Rodrigues, since the raw data from these studies were readily available to us), in the Brazilian territory among the Caboclos-river dwellers (Amazon forest biome, Amazonas State; 1995), the Krahô Indians (cerrado brushlands, Tocantins State; 1999) and the Quilombolas (area of transition between the cerrado brushlands and the pantanal wetlands in Poconé, Mato Grosso State; 1999).[1]

[1] The latter two EP studies were approved by the Ethics Committee of the Federal University of São Paulo (UNIFESP's Ethics Committee on Research n. 056/00). The biological resources and traditional knowledge associated with biodiversity (TK) referred to in this article are protected under the terms of the United Nations Convention on Biological Diversity (CBD), in force internationally since December 1993. Any individual or public or private entity who wishes to carry out scientific or technological investigations on the biological resources and TK referred to shall observe the requirements set forth by Articles 8 (j) and 15 of the CBD, as well as, in the case of Brazilian biological resources and TK, the requirements set forth by the Provisional Measure no. 2.186-16/2001, which regulates access to genetic resources, protection and access to TK and the sharing of benefits arising from the use of Brazilian TK and biological resources. The unauthorized use of these resources is an act of misappropriation, and subjects violators to administrative, civil and criminal penalties in Brazil.

Prescription ID number: Interviewee ID number:

Date and place of interview: Duration of interview:

A) Composition of the prescription/recipe

What is the name of the prescription/recipe?

How many different plants are present in the prescription?

How many different plant parts/ingredients are present in the prescription? [*Where more than one part of the same plant is included, count each separately*]

For each plant ingredient present in the prescription, record:
- collection ID number(s);
- vernacular name(s);
- part(s) used and their respective amounts in the prescription [*both as described by the interviewee and as described/measured by the researcher*];
- scientific name(s);
- voucher specimen number.

B) Therapeutic use

For what health problem/medical condition is the prescription used?

C) Preparation and storage

C1) Ingredients

For each plant ingredient, record whether the material is used fresh or stored before use.

If the material is stored, describe how it is stored (e.g. dried), the location and the storage conditions (e.g. in darkness, away from moisture).

For each plant ingredient, record whether the material is prepared before use?

If the material is prepared, provide details of the method(s) of preparation, including quantities and proportions of solvents where relevant.

C2) Prescription

How is the prescription prepared? [*Provide details of the method(s) of preparation, including quantities and proportions of solvents where relevant*].

Is the prescription used fresh or stored before use?

If the prescription is stored before use, describe how it is stored (e.g. dried), the location and the storage conditions (e.g. in darkness, away from moisture).
What is the dosage form (e.g. tincture, infusion, poultice, syrup, cigarette, etc.) of the prescription?

D) Route of administration

What is the route of administration (e.g. oral, topical, rectal, inhalation, etc.) of the prescription?

Are any routes of administration contraindicated for this prescription? If so, state which route and why.

E) Dose, dosage and duration of administration

What is the dose of the prescription as described by the interviewee? [*Include dose range where appropriate*].

What is the dose of the prescription as described/measured by the researcher? [*Include dose range where appropriate*].

What is the dosage of the prescription? [*Include dosage range where appropriate*].

What is the duration of use of the prescription? [*Include range where appropriate*].

F) Adverse/undesirable/unexpected effects of the prescription and its ingredients

F1) Traditional general knowledge on adverse/undesirable/unexpected effects.

Is this prescription, or any of its individual ingredients, associated with, or known or thought to cause any adverse/undesirable/unexpected effects ('side effects')?

If yes, provide the following details for each adverse/undesirable/unexpected effect:
- whether the adverse/undesirable/unexpected effect relates to the prescription or individual ingredients [*state which*];
- describe the adverse/undesirable/unexpected effect;
- the dose, dosage, duration of use of the prescription, or ingredient(s), associated with causing the effect if known;
- how long the adverse/undesirable/unexpected effect lasts.

F2) Personal experiences of adverse/undesirable/unexpected effects

Have you, your child or someone you know ever experienced any adverse/undesirable/unexpected effects ('side effects') or new symptoms after taking this prescription or any of its individual ingredients?

If yes, provide the following details for each adverse/undesirable/unexpected effect experienced:

- who had the adverse/undesirable/unexpected effect (you, your child, etc.); male/female;
- age of the person at the time of the adverse/undesirable/unexpected effect;

Fig. 1 Data items for collection during ethnobotanical/ethnopharmacological surveys for use in pharmacovigilance

- the symptoms of the adverse/undesirable/unexpected effect, how 'bad' they were, how long they lasted and what was the outcome (e.g. recovered, still the same, worse, person died);
- was any treatment taken/given for the adverse/undesirable/unexpected effect;
- whether the adverse/undesirable/unexpected effect related to use of the prescription or an individual ingredient(s) [*state which*];
- what symptoms/condition/reason the prescription/ingredient was being used for;
- the dose and dosage of the prescription, or ingredient(s), associated with causing the effect;
- how long had the prescription/ingredient(s) been taken before the adverse/undesirable/unexpected effect occurred;
- did the person stop taking the prescription/ingredient(s) because of the adverse/undesirable/unexpected effect(s)?

If so, what happened (e.g. improved, no change, worsened);

- were you/the person using any other medicines/new foods before or at the time the adverse effect occurred?
- when you/the person experienced the adverse/undesirable/unexpected effect, was it the first time you/the person had ever used this prescription/ingredient?
- if not, when/how long ago was it last used?
- on the previous occasion(s), was the same or a different amount taken? [*Give details*]

What happened on that/those occasion(s)?

- have you/the person taken the prescription/ingredient again since the adverse/undesirable/unexpected effect occurred?

If so, what happened (e.g. same/new/no adverse effect occurred);

- any other information considered relevant.

G) Cautions and Contraindications

G1) Cautions: interactions

Are there any other substances (e.g. other plant medicines, fungi, animal medicines, allopathic medicines) that should be avoided when using this prescription or its individual ingredients (e.g. because of the possibility of interactions occurring)?

If yes, record which substances and which ingredients are considered to interact, and the nature of the interaction.

2) Contraindications

Are there any contraindications to this prescription or to any of its individual ingredients, including, for example, use by pregnant/breastfeeding women?

If yes, for each contraindication, describe the contraindication and record whether it relates to use of the prescription or to an individual ingredient(s); state which ingredient where relevant.

If this prescription, or any of its individual ingredients, is/are used accidentally when contraindicated, is there any plant or other remedy that can neutralize the effect (i.e. act as an antidote)? If yes, record the name(s) of the plant(s) or other remedies, their preparation, dose and other details when used in this context.

G3) Poisonous parts

Are any other parts of the plant(s) that was/were used in this prescription (i.e. parts other than those used in the prescription) contraindicated for being poisonous? If yes, for each, record which plant and which plant parts are considered to be poisonous, the symptoms of poisoning, the quantity considered to be poisonous (for both adults and children, if known) and the route(s) of administration?

H) Food and/or sexual taboos

Do any food and/or sexual taboos relate to this prescription or any of its individual ingredients?

If yes, for each taboo, describe the taboo and record whether it relates to use of the prescription or to an individual ingredient(s); state which ingredient where relevant.

I) Other relevant information

Is there any other information about this prescription or any of its individual ingredients that you would like to mention?

Fig. 1 continued

2.1 Composition of the Prescription (Item A)

In any EB/EP studies, regardless of their focus, it is obvious that it is essential to establish to which traditional medicine(s) an interviewee refers. Likewise, in pharmacovigilance, one of the four essential components required to constitute a report of a suspected ADR is information on the suspected drug(s) taken.

With respect to traditional medicines, the primary information required for elucidation and registration of a 'recipe' or prescription refers to the vernacular name(s) of the plant or plants of which the prescription is composed and the specific part(s) used. Some 'recipes', such as 'Removing the Devil cigarette' described in our earlier studies [12, 13], have multiple ingredients (nine in this example) and it is important to obtain the necessary information on each.

Often the common name of a plant in itself provides further information; for instance, it may reflect a particular organoleptic characteristic, or a certain property, of the plant. *Chenopodium ambrosioides* L. (Amaranthaceae) is known in Brazil by the coastal caiçara fishermen as *caanema* (*kaa* meaning grass, and *nema* foul smelling), because this plant exudes a strong odour. In other cases, the name reflects a pharmacological activity or effect of a particular plant; for example, the literal translation of *caprankohirehô* (Euphorbiaceae) is leaf of 'turtle spine', describing its pharmacological effect – inducing 'slowness'. The Krahô Indians discovered a use for these plants after observing that when consumed by

deer, the deer became easier to hunt since they moved more slowly.

Thus, knowledge of the native language assists in translating common names of plants and understanding their meanings, which may relate to properties, uses and/or perceived effects. Nevertheless, it is extremely important to be mindful that the same plant can be recognized by various common names, and that the same or similar names can refer to different plants; incorrect nomenclature can lead to misunderstandings and accidents in use and creation of unreliable information. Accordingly, identification of prescription ingredients using their scientific name, under the Rules of the International Code of Botanical Nomenclature [14], is essential.

Collection of herbarium voucher specimens is also essential to enable scientific identification, since they can be validated by plant taxonomists. Furthermore, the voucher provides a physical link if, in the future, there are any taxonomic changes. In practice, full identification is not always possible since, at the time of field collection, only sterile plant material may be available, or the study may involve plant material sold in markets, which may consist of only dried plant parts.

In addition to establishing the precise ingredients of a prescription, it is also important, with respect to safety, to determine the quantity of each ingredient present, as well as its dose, dosage and duration of use (see also Item E [Sect. 2.5]). For example, quantitative information is particularly relevant when considering possible clinical outcomes in cases of poisoning, including accidental ingestion, and whether a particular prescription is appropriate for use in certain cases, such as for pregnant women. With respect to pharmacovigilance, quantitative information on the composition of a prescription and/or quantities ingested can be useful when undertaking causality assessments in cases of suspected ADRs, at least in respect of plausibility. For example, if a particular ingredient and, therefore, its chemical constituents are present in only trace quantities, are known to be poorly absorbed and have not previously been associated with adverse effects, then such information might lead to the determination that causality for this ingredient is 'unlikely' (provided all other elements of a causality assessment pointed to the same conclusion for this ingredient). This is not to say, however, that herbal ingredients and their constituent chemicals present in low concentrations and which have previously been considered to have a good safety profile cannot be responsible for adverse effects.

Establishing precise quantities, however, raises some challenges. Interviewees may state quantity numerically; for example, the number of leaves, seeds, flowers or fruits present in a prescription; as volume (for oils and latex); as weight for plant parts such as bark, root, tubercle, whole plant, resin, petiole and even small seeds/flowers/fruits; and in other ways.

Occasionally in EB/EP studies, interviewees describe the quantity of a plant part in terms of 'fingers' or 'a piece' particularly for bark and roots, or as 'a handful' (particularly for leaf material). Interviewees' use of such non-specific terms or proxy measures for quantity highlights the need for researchers to use an appropriate instrument, such as a balance, in order to measure the exact quantities of plant parts. For multi-ingredient prescriptions, such as "Removing the Devil cigarette", which comprises nine plants, the quantity and proportion of each ingredient need to be determined.

2.2 Therapeutic Use (Item B)

During EB/EP studies, the ingredients that constitute a certain recipe, and the reason for use of the recipe, are among the most important pieces of information to be recorded, since this information can allow the selections of specific ingredients for testing for specific disorders during pharmacological investigations. Often, the fieldwork researcher is able to establish a correlation between the medical terms used to describe complaints/ailments in the traditional medicine system with those used in conventional medicine. After translating the traditional medicinal terms used, it is desirable to group the complaints/ailments that the recipes are used to treat into categories according to the International Classification of Diseases (ICD) [15], such as diseases of the nervous system, diseases of the genitourinary system, diseases of the respiratory system and so forth. The participation of a physician in this translation/task, as well as their involvement in fieldwork, is highly desirable, but not always possible [16].

Sometimes, however, a correlation between indigenous and conventional medical terms is not possible since the aetiology and/or symptoms of some conditions, from an indigenous perspective, are very complex; for example, the cultural syndromes reported by some authors [17, 18].

From a pharmacovigilance perspective, it is important to know the medical/health condition of the patient prior to the use of traditional (and other) medicines so that consideration can be given as to whether a new symptom is a suspected ADR or part of the natural history of the existing illness. Accordingly, the field researcher needs to collect information on the symptoms/medical/health condition of the patient prior to use of traditional (and other) medicines (see Item F [Sect. 2.6] for collection of data on new symptoms/adverse effects).

2.3 Preparation and Storage (Item C)

Herbal medicines are prepared by indigenous communities as many kinds of traditional dosage forms – teas (infusion or decoction), tinctures, cigarettes, poultices, syrups,

juice – and using material that is fresh, dried or fermented. Variations on these classic dosage forms, even new types of preparations, can also be observed during field work. For example, one formulation is achieved by placing the leaves of a certain plant in a bottle with sugar and water; after being stoppered and sealed, the bottle is submerged in a river for 3 days and then exposed to sunlight for a further 3 days before the preparation is ready for consumption. Soaking, changes in temperature, and other 'treatments' can affect the extraction of, or degrade, certain constituents [7, 19]. The exact quantity of water or other solvent (and its strength, for solvents other than water) utilized in the preparation process should also be noted, as well as the proportions of solvent(s) and plant part(s). This information can be used in calculating the quantity of an ingredient ingested.

The dosage form and method of preparation can influence the composition of a 'recipe' both qualitatively (presence or absence of certain constituents) and quantitatively (higher or lower concentrations of certain constituents), and this can have implications for safety. For example, in traditional Chinese medicine, the toxic alkaloid content of the *Aconitum* species is partly decomposed during processing [20]. In Africa and South America, processing of the traditional food cassava (*Manihot esculenta* Crantz) removes the toxic cyanogenic glycoside constituents [21].

It is also important to determine whether the plants utilized in the recipes are fresh, collected just before their preparation or stored prior to use. Where material is stored, it is important to identify any efforts undertaken to avoid microbial contamination; for example, whether the plant material is dried/dehydrated or manipulated in any other way, and how and where it is stored, such as in a dry and well-ventilated place. This type of information can be useful in determining whether a new symptom is a suspected adverse reaction arising from the pharmacological effects of the plant, or a response to ingestion of plant material contaminated with bacteria or fungi, i.e. related to poor quality.

2.4 Route of Administration (Item D)

Several routes of administration for traditional medicines can be cited by interviewees during EB/EP surveys: oral (for infusions, decoctions, tinctures, fresh material, syrups, juices, fermentations), topical (for compresses, poultices, massages, baths, gargles), inhalation (cigarettes, fumigants, infusions, decoctions) and rectal (infusions, decoctions). Typically, most attention from researchers is given to the oral route, but it is important that the disciplines of both ethnopharmacology and pharmacovigilance also consider the topical, rectal and inhalation routes, since they too are recurrent in traditional medicine. Furthermore, it may be necessary to consider whether a particular type of preparation is administered by more than one route, either intentionally or consequentially. For example, the attribution of anxiolytic activity to essential oils may be related not only to the oral or topical route; inhalation of volatile compounds may induce stimulative or sedative effects in mice [22]. In humans this may also occur during the ingestion of hot tea where active principles, such as essential oils, volatilize and may thus be inhaled [13]. Similarly, baths are also an important vehicle in traditional medicine for administration via the topical and inhalation routes.

In some cases, certain routes of administration are contraindicated and this type of information obtained in EB/EP studies can provide some information on possible, or at least, perceived, toxicity. For example, *Vernonia herbacea* (Vell.) Rusby (Asteraceae) is used topically – Krahô Indians massage their children's legs with the root juice, three times a day for 1 week per month – but interviewees explain that this prescription cannot be ingested orally due to its toxicity (Rodrigues E, unpublished observations). Krahô Indians also explain that the latex of the fruit from *Qualea parviflora* Mart. (Vochysiaceae) is utilized topically as a medicine, but its ingestion is not allowed because it is suspected to be poisonous. In another example, Indians place grated tubercles of *Cissampelos ovalifolia* DC. (Menispermaceae) on snake bites, claiming that an analgesic effect is evident within half an hour; however, it is also explained that 'if the water of the tubercles is ingested, someone can die', since the plant is a 'human poison'. These claims are supported by preclinical research; Gorinsky et al. [23] describe neuromuscular-blocking and local anaesthetic activities for warifteine hydrochloride, an alkaloid isolated from the roots of *C. ovalifolia*.

2.5 Dose, Dosage and Duration of Administration (Item E)

During EB/EP studies, the dose, dosage and duration of use of a prescription should be recorded. Information on any ranges should also be noted (for example, 2–4 cups, 3–4 times daily, for 6–8 weeks) since the upper limit may be indicative of a maximum tolerated dose, dosage or duration of use.

Establishing as accurately as possible the dose, dosage and duration of use recommended by members of an ethnic group for a plant or recipe is very important as it could be useful in undertaking causality assessments (see Item A [Sect. 2.1]) and to guide safe use of herbal medicines. In particular, such quantitative information, together with information on outcomes, can be used to inform the likelihood of other users of the plant experiencing adverse

reactions, i.e. the dose-relatedness of the reaction can be considered. To obtain information in this context from interviewees, the researcher should explore whether or not interviewees have used different doses or dosages of a certain prescription, for what purpose and what, if any, were their experiences of adverse effects or new symptoms. Some examples from completed work are given below and in Sect. 2.5.1.

In Brazilian indigenous medicine, the roots of *Bauhinia* cf. *stenocardia* Standley (Fabaceae s.l.) are crushed and boiled and one cup of this preparation is ingested four times a day; it is said that the preparation should not be used for more than 2 days, or it could be toxic. The roots of another plant, *Julocroton humilis* Didr. (Euphorbiaceae), must be boiled in water and one spoonful ingested daily for medicinal purposes; however, Krahô Indians explain that higher doses may be fatal. Another example comes from *Tabebuia ochracea* (Cham.) Standley subsp. *ochracea* (Bignoniaceae). Indigenous knowledge is that its bark must be immersed in water and ingested twice a day for medicinal purposes, but that this prescription must be consumed with caution since it is a 'strong medicine'.

2.5.1 Special Patient Groups: Children and Older Patients

Likewise, it is important to determine from interviewees whether there are different dose recommendations for adults, children, older patients or other special patient groups. Some plants are considered to be 'strong remedies', and interviewees explain that they may only be consumed by children and older patients in reduced doses, or not at all [24].

Examples of plants for which dose restrictions are recommended for children include *Piper tuberculatum* Jacq. (Piperaceae). Krahô Indians explain that a handful of the flowers of this plant should be boiled in two glasses of water, until only one glass remains; the tea must be covered and ingested when cool. Adults must ingest one glass twice a day, but children should ingest lower amounts depending on their age. For *Diplusodon* sp. (Lythraceae), children should consume only one medium-sized spoonful daily of a decoction prepared from the tubercles. Another example relates to the method of preparation of the dose for administration to children: the leaves of both *Oxalis densifolia* Mart & Zucc. ex Zucc. (Oxalidaceae) and *Odontadenia lutea* (Vell.) Markgr. (Apocynaceae) should be chewed by a parent before the leaf juice is given to their child for medicinal purposes.

With respect to older patients, some plants that it is said should be used only with caution (i.e. at reduced doses) include *Psittacanthus robustus* (Mart.) Mart. (Loranthaceae) and *Helicteris muscosa* Mart. (Sterculiaceae).

2.6 Adverse/Undesirable Effects of the Prescription and Its Ingredients (Item F)

The purpose of the questions in this section is 2-fold. The first part aims to elicit information on the safety profile of traditional herbal medicines that is embedded in traditional knowledge; it is the collective understanding about the harmful and undesirable effects of plants that has evolved through the clinical experiences of the indigenous people who have been using these natural resources for centuries and which is passed on through oral traditions. One example is *Rudgea viburnoides* (Cham.) Benth. – Rubiaceae, a plant whose leaves are ingested as tea by a Quilombola group. A native explained possible effects on ingestion of this plant: "*although it acts as a medicine, it diminish blood pressure and also provoke loss of sexual desire*". The interviewee also explained that naturally hypotensive individuals should avoid this plant, and find a substitute.

A related point of interest from field work among shamans is the observation of two 'types' of knowledge. One is specific: knowledge that the shamans utilize to effect a cure, or to antagonize witchcraft from shamans of other villages; this knowledge is not shared with anyone, even their wives. The other type is a 'diffused knowledge', since it is disseminated among members of the village or community, particularly among subgroups at risk of harm in relation to the item of knowledge. For example, information on plants which may cause abortion must be disseminated (by midwives, healers, shamans) among the individuals of the villages/communities, particularly the women. The second part of this section of the tool aims to identify personal experiences (including those of close family members, such as a parent reporting an adverse effect experienced by their child) of adverse, undesirable or unexpected effects associated with the use of traditional herbal medicines. It is essentially the collection of spontaneous reports of suspected ADRs in an intensive manner (i.e. a targeted rather than a passive approach). The proposed tool also asks interviewees about experiences of adverse effects experienced by others ('someone you know') because, in some cultures, and particularly in traditional ethnic groups, the 'responsibility' for and knowledge of others' health is broader. In EP studies, interviewees often are shamans, healers or midwives; these individuals are the holders of the traditional knowledge on the benefits and harms of traditional medicinal plants, and that is why they are responsible for the health state of members of their village or community and why they are informed if adverse, undesirable or unexpected effects occur following use of traditional medicines.

Asking about personal experiences of adverse effects in a detailed manner has the potential to identify new or

previously unrecognized adverse effects. Such new information on harmful effects (for which there is no traditional knowledge) could arise for several reasons: a prescription could be used for a condition for which it had not previously been used, plant ingredients could be used in new combinations, there may be a change in the quality of the plant material or its method of preparation or the adverse effect may simply not have been associated previously with the use of a particular plant or prescription.

In pharmacovigilance, the four basic elements required for a valid report of a suspected ADR are information on the person experiencing the suspected ADR, the reporter, the suspected 'drug(s)' taken and the nature of the adverse effect. Additional questions (item F2), while adding to the length of the interview, can provide information that allows a formal causality assessment to be undertaken. Information relating to de- and re-challenge with the suspected herbal medicine (i.e. observations on stopping and, where it occurs, restarting treatment with the suspected drug[s]) can be particularly informative.

2.7 Cautions and Contraindications (Item G)

2.7.1 Interactions between this Prescription, its Ingredients and Other Substances (e.g. other Plants/ Phytomedicines, Fungi, Animal Medicines, Allopathic Medicines)

Many herbal medicines (whether single- or multiple-ingredient preparations) pose no safety concerns when used according to the recommended dose, dosage and duration of administration. However, in some cases, if a herbal medicine is used concurrently with certain other herbal medicines, foods or other substances, including conventional medicines, or if the ingredients in a herbal medicine prescription are changed, drug interactions between these substances can occur. Such interactions can be pharmacokinetic or pharmacodynamic. In some cases, such interactions can be beneficial; for example, where one substance reduces the toxicological effect of another [25]. Another example is the mind-altering beverage *ayahuasca* (also known as *caapi, natema, pindé* or *yajé*) utilized by Brazilian Indians. The composition of this beverage includes some species of the genus *Banisteriopsis* (Malpighiaceae), mainly *Banisteriopsis caapi* (Spruce ex Griseb.) Morton and *Banisteriopsis inebrians* Morton, together with *Psychotria viridis* R. et P. The pharmacological activity of the drink depends on a synergistic interaction between some of their constituents; the *Banisteriopsis* species contain β-carboline alkaloids, mainly harmine, harmaline and tetrahydroharmaline, which inhibit the enzyme monoamine oxidase, thereby potentiating the action of N,N-dimethyltryptamine (DMT) present in *P. viridis* [26].

To date, and in this article, most emphasis has been on adverse effects of interactions. Since each herbal ingredient in a prescription contains hundreds of chemical constituents, the potential for interactions with multiple-ingredient prescriptions may be substantial. Moreover, as qualitative and quantitative variability can occur in both fresh and processed herbal material, understanding cases of suspected interactions associated with herbal medicines and developing knowledge in this area is a difficult and complex task.

Thus, to contribute to this work, in EB/EP studies it is important to establish from interviewees whether there is any knowledge on substances with which a particular plant or prescription should or should not be used; in this paper we are most interested in substances with which a plant or prescription should not be used and the reason for this, but it may also be enlightening and prudent to collect data on substances with which a particular plant or prescription is considered suitable for use.

In traditional medicine, it is common for multiple-ingredient, multiple-source preparations to be used. In Brazil, Afro-descendants and other cultures, very often utilize several plants in a single prescription [24]. Among some Quilombolas, up to ten plants may be included in a single prescription; while river dwellers from Jaú National Park in the Brazilian Amazon rainforest utilize up to five ingredients of plant, animal or mineral origin per prescription [27, 28].

On the other hand, Brazilian Indians typically use only one plant ingredient per prescription; they avoid using combinations of plant ingredients because they are not familiar with the possible interactions between them [24]. Krahô Indians rarely include several plant ingredients in a single prescription and, if they do, they utilize two at most. They explain that these prescriptions are used only when a 'strong effect' is required. In these cases, both plants are known as 'partners' and have the same indigenous name, although frequently they belong to different taxonomic families; also, one plant is considered to be 'stronger' than the other, according to interviewees. For example, the roots of two plants from the genus *Cipura* (Iridaceae) are used together to combat diarrhoea.

2.7.2 Contraindications

Some plants are contraindicated altogether in certain special patient groups because of the actual or perceived risk to health. Collecting full information on such contraindications, including the plant ingredient(s) considered to be implicated, the nature of the contraindication, and the existence and details of any antidotes can also inform safe use and allow further examination and, possibly, identification of plausible explanations. Some examples where information on contraindications has been collected during EB/EP studies are given in Sects. 2.7.3, 2.7.4, and 2.7.5.

2.7.3 Pregnant Women

In our previous publication from work undertaken in Brazil, 37 plants are listed that should be avoided by women during pregnancy [24]. These plants were cited during EP surveys carried out with three different Brazilian cultures: Krahô Indians, Afro-descendants and Caboclos-river dwellers. Of the 37 plants, 13 were described by the interviewees as having abortive properties; 10 were cited as contraceptives; 6 as being utilized to facilitate labour; and the remaining eight plants were said to be contraindicated in pregnant women.

From data presented previously [24], a crude comparison of the number of plants considered to be contraindicated in pregnant women ($n = 37$) with the number of plants with other kinds of use restrictions (poisonous to humans and/or animals [$n = 10$], those that should be prescribed in reduced doses for children and older patients [$n = 10$]) suggests that knowledge concerning use restrictions in pregnancy is richer or, at least, recalled better. If this observation is correct, there are several possible explanations; there may be an abundance of plants in nature that are harmful if used during pregnancy and/or, because pregnancy is a health condition that requires caution, many types of restrictions arise, including avoidance of agents used as abortifacients, contraceptives, or to aid or stimulate parturition. This is supported by interviews with representatives from several Brazilian cultures, such as Afro-descendants, Caboclos-river dwellers and Krahô Indians, who report that almost all 'bitter' tasting plants should be avoided by pregnant women [24]. Other EB surveys report similar findings [29]. To understand this, one needs to consider the logic of native medicines; plants with a bitter taste are considered to be 'strong medicines' and are thus associated with causing 'side effects' [30–33]. There may be a scientific basis for these beliefs – preliminary clinical studies have described associations between bitter taste and nausea [34] and an increase in bitter-taste perception and severe vomiting in pregnancy [35].

2.7.4 Children

Two plants used medicinally by adult Krahô Indians but which are contraindicated in children are teas made from the leaves or roots of *Ouratea* cf. *castaneifolia* (DC.) Engl. (Ochnaceae) and cigarettes made from the leaves or roots of *Aeschynomene* cf. *mollicula* Kunth (Fabaceae) s.l. The reason for the contraindication is not known.

2.7.5 Other Examples of Contraindications

The teas of *Aniba canellila* (H.B.K.) Mez (Lauraceae), *Cymbopogon citratus* (D.C.) Stapf. (Poaceae) and *Davilla elliptica* A. St.-Hil. (Dilleniaceae) are said to be contraindicated in men because they may cause loss of or reduction in virility. Several plants – *Ouratea* sp. (Ochnaceae), *Ayenia* sp. (Sterculiaceae) and *Heteropterys aphrodisiaca* O. Mach (Malpighiaceae) – used by Quilombolas for adaptogenic-like effects [12] are said to be contraindicated in people with kidney problems. The lianas *Tephrosia sinapou* (Buc'hoz) A Chev. (Fabaceae) s.l. and *Serjania* sp. (Sapindaceae), used as ichthyotoxic agents by Krahô Indians, are said to be contraindicated in humans; moreover, pregnant women are not allowed to consume fish that has been caught using these plants.

2.7.6 Antidotes for Plants Consumed when Contraindicated

This question aims to identify whether or not traditional knowledge exists on antidotes for plants consumed (accidentally or otherwise) when contraindicated. While it is not a simple process to develop this type of knowledge, there are some historical examples. The ingestion of large quantities of anticholinergic compounds, such as atropine and scopolamine, present in *Brugmansia suaveolens* (Humb. & Bonpl. ex Willd.) Bercht. & C. Presl and *Datura stramonium* L., can be reversed by physostigmine, present in the Calabar bean or Esère nut (*Physostigma venenosum* Balf. f.), which inhibits acetylcholinesterase (and thus re-establishes cholinergic activity) [36].

2.7.7 Are Any Other Parts of This Plant Considered to be Poisonous or Otherwise Harmful in Any Way?

One of the features of medicinal plants is that the chemical constituents responsible for the plant's pharmacological effects are typically present in only a specific part or parts of the plant and, therefore, it is this part or parts that are used medicinally. Likewise, a certain part or parts of the plant may contain toxic constituents and should be avoided. Establishing whether or not there are other parts of the plant (i.e. other than those used medicinally) that are considered to be harmful can be useful.

As harvesting and collection practices may not always meet recognized quality standards, it is possible that plant material from 'undesirable' parts of the plant can enter the production chain, or, where collection is on a local scale, individuals may simply collect the wrong plant part either accidentally or through ignorance.

2.8 Are There Food and/or Sexual Taboos Relating to this Prescription? (Item H)

For some plant prescriptions, their use requires adoption of a special diet and restrictions on consumption of certain foods; in some cases, it is also considered necessary to avoid

sexual activity. In interviews with Brazilian Indians, 17 plants were named that cannot be ingested concurrently with consuming 'heavy foods' (mainly meat and fat) and being sexually active. Specifically, some Krahô Indians explained that if an individual needed to use the tubercle of *Helicteris muscosa* Mart. (Sterculiaceae) for medicinal purposes, fatty foods should not be consumed simultaneously. Among Quilombolas the same instruction was reported with respect to other plants, such as *Siparuna guianensis* Aubl. (Monimiaceae) and *Isostigma grandifolia* Less. (Asteraceae).

These EP data are important since they raise the question whether or not these foods do interact with these plant medicines in some way and, if so, what is the mechanism for the interaction. One hypothesis for the food taboos described is that avoiding fatty foods and sexual activity could have some relation to body metabolism. On the other hand, the explanation for these instructions and behaviours could be non-physiological, i.e. they could be underpinned by spiritual or supernatural beliefs.

3 Strengths and Limitations

There are several strengths and limitations both to the content of the proposed tool and to its application in EB/EP and pharmacovigilance studies.

To our knowledge, this is the first tool that has been proposed to guide and assist collection of data relating to safety of traditional medicines and prescriptions in EB/EP studies, and it serves as a starting point for discussion and further work. The tool has been developed to collect detailed information on traditional herbal medicine prescriptions, including their ingredients, preparation and administration, and their safety profile, including contraindications, adverse effects and interactions, and use in special patient groups. It is intended to operate as an interview guide (not as a questionnaire for interviewees to complete), and includes both closed and open questions in an attempt to provide the flexibility interviewers (and interviewees) may require in EB/EP studies. The development of the tool is grounded in data from EB/EP studies with cultural groups in Brazil; moreover, it includes some questions similar to those used in national spontaneous reporting forms for collection of data on suspected ADRs.

An important limitation of the proposed tool is that (at present) it is designed only to collect information relating to plant ingredients of traditional prescriptions. It is recognized that some traditional prescriptions may include or comprise entirely ingredients of animal, mineral or other origin; such ingredients have specific characteristics for which data need to be collected. This may be addressed in future work.

Although the tool aims to assist systematic and comprehensive collection of data, rarely are all the elements of a prescription (plant part[s], preparation method and storage, doses and dosages, and so forth), as well as its effects, described or reported and with the same level of detail by all interviewees in a community. This can complicate analysis of EB/EP data since it is difficult to make general statements from the information and, at the same time, exceptions must be taken into consideration. In such cases, methods of analysis, such as calculating indices of agreement, may be useful strategies [8]. Moreover, when analysing data collected using the tool, it is important to consider that even if a particular plant is not known to be associated with safety concerns in the ethnic group being studied, this may not necessarily be the case if the plant is ingested by individuals of a different ethnicity, because, for instance, of some genetic difference.

Applying the tool may become cumbersome where a prescription has multiple ingredients, not least because of the volume of data to be collected and the necessary repetition of questions. In these cases, tabulating the information, particularly for items A and C1, may assist data collection.

Ultimately, the quality of the data collected will always, in large part, depend on the quality of the data provided by interviewees/informants, and comprehensive answers across all sections of the tool will be the ideal rather than the norm. There may be a reluctance among (some) interviewees to reveal the uses of certain medicinal plants, or to reveal certain uses; whether there could be an equal reluctance to reveal the adverse effects of certain medicinal plants, or certain adverse effects, is yet to be explored. These and other issues, such as the cultural appropriateness of a questionnaire tool, have previously been identified as inherent problems with questionnaire surveys in ethnopharmacology [11].

In several respects, the disciplines of EB/EP and pharmacovigilance are already familiar with working with incomplete data. Since the collection of data on adverse effects and 'restricted uses' has been limited to date, there may be difficulties for EB/EP researchers in interpreting 'lay' descriptions and in learning and applying new terms and methods of pharmacovigilance in their work (and vice versa). In either case, researchers are encouraged to seek specialist expertise from the relevant discipline and all research involving indigenous people and resources should comply with and remain mindful of protections on biological resources and traditional knowledge.

Field testing of the tool is necessary to examine the issues mentioned above and to identify other strengths and weaknesses. Constructive criticism to the authors is welcomed.

4 Conclusions

This paper draws on the disciplines of ethnobotany/ethnopharmacology (with their emphasis on the composition, preparation and uses of traditional plant medicines) and pharmacovigilance (with its focus on identifying and preventing adverse effects of medicines), and intercalates elements of each to develop a concept of ethnopharmacovigilance for traditional herbal medicines.

With respect to EB/EP studies, ethnopharmacovigilance opens up a potentially rich new area for data collection, one that may both complement and extend the focus of standard EB/EP studies. Plants identified as having 'strong' or toxic properties could potentially provide new leads for bioactive compounds (on the basis that toxic constituents have pharmacological effects, albeit undesirable ones) or the information could be used to aid selection of plants (and ultimately doses, types of preparation and so forth) for further investigation in phytochemical, EP and even clinical studies. A majority of plants mentioned in this article has not undergone basic phytochemical and preclinical testing, and the few that have been studied have been investigated in the context of potential benefit, rather than adverse, effects.

From a pharmacovigilance perspective, an extension into EB/EP studies brings the possibility of broadening and deepening knowledge on the safety profile of traditional herbal medicines through the collection and collation of traditional knowledge on methods of preparation and administration details, adverse effects, cautions and contraindications and so forth. Furthermore, there is the opportunity of gathering spontaneous reports of suspected ADRs associated with traditional herbal medicines, at least in a targeted approach for specific prescriptions or plant ingredients and, thus, a means of identifying signals of safety concerns for these traditional preparations. Although several countries (such as Brazil), where the use of traditional medicines by indigenous people is embedded in culture, have a national system for collection of reports of suspected ADRs associated with medicines, this system is unlikely to be accessed by indigenous people. Moreover, in many other countries where the indigenous people have a cultural relationship with natural resources, there is no national pharmacovigilance system or one that is only in the earliest stages of development. While this paper focusses on Brazilian natives (mainly indigenous knowledge), ethnopharmacovigilance could also be applied to other ethnic groups, even those living in urban situations; for example, Asian immigrant groups in the UK, for whom there may be additional barriers to using the national ADR reporting scheme. Whether the proposed tool can yield data sufficiently rich and of an appropriate quality of application of EB/EP (e.g. data verification and quantitative analysis tools) and pharmacovigilance techniques (e.g. causality assessment and data mining for signals of safety concerns) requires field testing.

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