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Herbal medicine for epilepsy seizures in Asia, Africa and Latin America: a systematic review

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ABSTRACT

Relevance: More than 70 million people suffer epilepsy worldwide. Low availability of anti-epileptic drugs, side-effects and drug-resistant epilepsy affect the quality of life of persons with epilepsy in countries with a poorly developed health system. Herbal medicine is frequently used for this neurological condition.

Objectives: The main objective was to provide a detailed analysis of Herbal Medicine used for neurological conditions related with epilepsy in Asia, Africa and Latin America. More broadly, this study aims to highlight species with assessed efficacy (cross-cultural use, pharmacological effects on models of epileptic seizures) and safety (toxicological data in laboratory) information, in order to point out species of interest for further studies. A critical assessment of models used in pharmacological evaluations was done.

Materials and methods: The systematic search for Herbal Medicine treatments for epilepsy was performed considering all the articles published until February 2017 through three scientific databases. It was made with MeSH terms and free text defining the epilepsy seizures and plant species. We included studies carried out in Asia, Africa and Latin America. All articles reporting the use of Herbal Medicine to treat epilepsy seizures and/or their pharmacological evaluation were retained for further analysis.

Results: The search yielded 1886 articles, from 30 countries. Hundred and six articles published between 1982 and 2017 were included, corresponding to a total of 497 use reports for 351 plant species belonging to 106 families. Three hundred and seventy seven use reports corresponding to 264 species in ethnopharmacological surveys and 120 evaluation reports corresponding to 107 species were noted. Twenty-nine reports, for 29 species, combined both ethnopharmacological and pharmacological evaluation. Fifty eight studies originated from Africa, 35 studies from Asia and 18 from Latin America. Highest use report was noted for rhizomes of *Acorus calamus* L. (12 use report in 1 country) and leaves of *Bacopa monnieri* (L.) Wettst. (8 use report in 2 countries). Therefore these species display the highest use convergence. Regarding pharmacological evaluation most studied species were: *Leonotis leonurus* (L.) R.Br. (4 evaluation reports in 1 country), *Uncaria rhynchophylla* (Miq.) Miq. ex Havil. (3 evaluation reports in 2 countries) and *Calotropis gigantea* (L.) Dryand. (3 evaluation reports in 1 country). *In vivo* models of chronic epilepsy were more relevant than *in vitro* models or chemical models inducing acute seizures for pharmacological assessment.

Conclusion: Species with the highest use report were not those with pharmacological evaluation. It will be pertinent to assess the pharmacological effects and safety of medicinal plants used mostly by traditional healers on predictive models of seizures.

Key words: epilepsy; seizure; herbal medicine; medicinal plant; Asia; Latin America; Africa; pharmacological models.

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1. Background

Epilepsy is a disease of the brain defined by at least two unprovoked seizures occurring more than 24 hours apart or a diagnosis of an epilepsy syndrome (Fisher et al., 2014). This devastating multi-causal chronic disease is characterized by recurrent spontaneous seizures (a seizure is a transient occurrence signs due to abnormal excessive or synchronous neuronal activity in the brain) that affects 70 million persons worldwide, 80% of them lived in low and middle income countries (Ngugi, Bottomley, Kleinschmidt, Sander, & Newton, 2010) where, in many cases, epilepsy remains untreated (Newton & Garcia, 2012). The disease is classified between 3 etiologies; genetic, structural/metabolic, of unknown cause and different types can be found. Epilepsy seizures are categorized in generalized (convulsive seizures, absences) and focal (motor, partial, complex, sensitive and secondarily generalized) seizures. Some epilepsies cannot be classified into generalized or focal, as temporal lobe epilepsy, generalized tonic-clonic seizures with generalized spike-wave, both focal impaired awareness seizures and absence seizures in a patient. Anti-epileptic treatment is based upon the use of drugs according to the type of seizures. All anti-epileptic drugs (AEDs) are synthetized, none are derived from natural products. Most commonly prescribed AEDs are phenobarbital, carbamazepine, phenytoin and sodium valproate. Phenobarbital is a GABA system activator at pre- and post-synaptic level whereas sodium valproate has a double mechanism: potentiator of GABA transmission and inhibitor of voltage-dependent neuronal calcium and sodium channels. Carbamazepin is an antagonist of cyclic adenosin receptors and phenytoin acts as a reductor of the automatism of neuronal hyperexcitability. The wide variety of mechanisms of action of AEDs makes it possible to target seizures with a different molecular mechanism. Association of anti-epileptic drugs might not be recommended Finally, about 30% of persons with epilepsy (PWE) are drug-resistant, representing a socioeconomic burden at the individual, familial and societal levels (Forsgren, Beghi, Oun, & Sillanpää, 2005). Moreover, these drugs are known to present many side effects such as sedation, hepatotoxicity, anxiety and depression, and only few of them can be administered to pregnant women (lamotrigine, levetiracetam, phenytoin and oxcarbamazepin) are the most tolerated whereas sodium valproate must be avoided). Epileptic condition is linked to an increased risk of depression, anxiety as well as impaired quality of life due to stigmatization, mental and physical impairment, work absenteeism, work-related accident, poor work efficiency and family dysfunction (Lee et al., 2005).

Most of the time, in countries with a less developed health system, a high treatment gap is registered (Harimanana et al., 2013; Moyano et al., 2014). In these countries, it has been demonstrated that this gap of treatment and the high reliance on TMC (traditional and complementary medicine, according WHO definition) lead PWE to use non-conventional treatments and more specifically Herbal Medicine (HM). Moreover, it has been showed that traditional healers know treatments to control epilepsy seizures (Auditeau et al., 2018; Keikelame & Swartz, 2015). A need for active health care participation, lack and dissatisfaction with occidental medicine may also motivate PWE to pursue TMC over conventional treatments. Infectious agents as bacteria (meningitis), parasites (neurocysticercosis, malaria) or convulsive fever (especially in children) can cause seizures and be confused with epilepsy. In these cases, traditional medicine provides plants that can be labelled as anti-epileptic although they actually provide anti-convulsive or anti-infectious activity. To date, few data are available on the use and effects of HM to actually manage the disease “epilepsy”. In order to better understand the use, safety and pharmacological effects of HM in epilepsy seizures, we conducted an exhaustive systematic review on this topic.

The main objective of this review was to provide a detailed analysis of medicinal species traditionally employed to control epilepsy seizures in tropical and sub-tropical areas of Asia, Africa and Latin America. The pre-clinical pharmacological evaluation of HM, on efficacy and safety, through appropriate *in vitro* and *in vivo* testing was also documented. Finally, this review aims at giving data in order to build recommendations or to improve national medicinal plant policies about the use and evaluation of some species of interest.

2. Methodology

2.1 Search strategy

The systematic search on Herbal Medicine treatments for epilepsy seizures was performed considering all the articles published until February 2017 through Medline (Pubmed), Science direct and Ref doc for the electronic research. Manual research was completed in the Paris Descartes Faculty of Medicine (France), the "Institut Francophone de Médecine Tropicale" (Vientiane, Laos), the "Universidad de Piura" (Peru) and the "Institut d'Epidémiologie Neurologique et de Neurologie Tropicale" (IENT, Limoges, France) libraries. The IENT bibliographic resource gives access to original writings, with comprehensiveness for the African continent.

Systematic search was made considering 2 methods; a research with "MeSH terms" and a research "free text" terms. First, we defined the MeSH terms related to species: "phytotherapy", "medicinal vegetal species", "herbal medicine" and "tropical vegetal species". Then, the MeSH terms related to epilepsy seizures were included: "generalized epilepsy", "partial epilepsy", "tonic-clonic epilepsy", "myoclonic epilepsy", "temporal lobe epilepsy", "frontal lobe epilepsy" and different etiologies "idiopathic epilepsy", "post-traumatic epilepsy". Each MeSH term defining disease was combined with each MeSH term designing species, separated by "AND". For free text, we used the word "epilepsy" to define the disease AND the word "medicinal plants" OR "herbal medicine" to define plants.

2.2 Eligibility criteria

A screening of article titles was first performed, and then eligible abstracts were read to determine the extent to which they met the eligibility criteria. Abstracts that met the inclusion criteria were retrieved and the full text articles were studied.

2.2.1. Inclusion criteria

To be eligible for the review, studies had to meet the following inclusion criteria:

(1) Bibliometric criteria: To cover the years until 2017, to be an original publication and to be published in English, Spanish or French,

(2) Study setting criterion: To come from tropical or sub-tropical areas (both sides of the Tropic of Cancer and Capricorn) of Asian, Latin American or African countries,

(3) Types of studies criteria:

- To report and document the use of HM to control epilepsy seizures (classified as ethnopharmacological references: publications reporting the use of medicinal plants with scientific determination (e.g. Chassagne et al., 2017)),

- To describe the pharmacological evaluation of HM in models considered to be relevant for epilepsy (classified as pharmacological evaluation articles: publications based upon anti-epileptic *in vivo* or *in vitro* models (e.g. Löscher, 2011)). Chosen studies had used validated tests for pharmacological evaluation.

(4) Botanical determination criteria: Only papers in which are mentioned, at a *minimum*, the preparation of herbarium samples to proceed to identification, the locality where the sample were collected and the names of collectors were included. Papers with taxonomical determination based upon identification keys, floras, field manuals or other reference resources cited, and studies providing identification with the help of botanical authorities (name of the expert and date of determination) and vouchers deposited in a Herbarium were integrated,

(5) Nomenclature: We checked all plants in The Plant List and we added standardized names from the list into the main text, tables and figures, following the current recommendations (Rivera et al., 2014),

(6) Clinical criterion: To report only traditional local practices regarding epileptic seizures described as tonic-clonic seizures associated with a loss of consciousness (other studies with etiologies such as febrile seizures, infantile seizures, syncope, toxic seizures, etc. were excluded),

(7) Legal criterion: To provide an ethical committee or people's protection committee approval.

2.2.2. Exclusion criteria

Studies meeting the following criteria were excluded:

(1) To include participants with others neurological diseases,

(2) To consider the evaluation of allopathic or homeopathic products, nutritional supplemental which were not Herbal Medicine,

(3) Not to mention reference to herbarium samples or to give inaccurate voucher specimen details or no details how specimens were identified,

(4) To provide incorrect botanical nomenclatures, detected through the specialized website The Plant List,

(5) To deal with remedies based on chemical, animal, mineral or pharmaceutical substances.

2.3 Data collection

All ethnopharmacological or ethnomedical information from Asia, Africa and Latin America countries linked with antiepileptic plant uses was collected.

For each species, a use report (defined as the number of citation of this species to control epilepsy seizures when browsing the overall literature) and an evaluation report (defined as the number of pharmacological tests performed on this species) were used in order to highlight use convergence and most studied species.

The following data were collected:

- Genus, species and family of the species mentioned in the publication. Standardization and actualization of the plants name was performed through website: http://www.theplantlist.org/.

- Continent, country in which the study was conducted with the description of the plant environment.

- Other indications of the species, especially if it had other indications in diseases of the Central Nervous System.

For each type of studies, we collected specific data:

- For articles presenting quantitative data allowing to assess the importance of the use of species to treat epilepsy seizures: parameters relevant to quantification (type of indicators used, number of people interviewed, etc.) were noted, as well as results. Many indicators first used by ecologists were applied in the surveys (Hoffman & Gallaher, 2008).

- For articles listing the use of HM to control epilepsy seizures without quantified data: part of the plant used, mode of preparation and administration were included in the database.

- For *in vitro* pre-clinical studies: the part of the plant used, type of extracts, name of models, doses, results and reference anti-epileptic drugs (AEDs) were reported.

- For *in vivo* pre-clinical papers: the part of the plant used, type of extract, name of models, administration route, doses, results and reference AEDs were noted, as well as indication of toxicity if the studies mentioned it.

Data were managed in an *ad hoc* database, using software Excel® and Access®.

2.4 Data analysis

The primary outcome was the use report of the species. Secondary outcomes were quantitative indicators of use (for ethnopharmacological studies) and seizure parameters (e.g. duration, latency and frequency of seizures), type of model used (for *in vitro* and *in vivo* trials).

Studies reporting the same outcomes measures were analyzed together. Data from ethnopharmacological surveys and trial intervention were pooled separately.

In order to identify and select species with high use convergence, their use report was evaluated.
For ethnopharmacological surveys, it was defined by the expression:

$$One\ use\ report\ = One\ species + One\ part\ of\ plant + One\ geographical\ location$$

If the same species/part of plant was cited in two different publications or in two different geographical locations, we counted 2 use reports.

In the case of articles with pharmacological models, we considered the use report as:

$$One\ evaluation\ report = One\ species + One\ part\ of\ plant + One\ preclinical\ test$$

The statistical analyses were performed using Stata 12® software (Stata Corporation, College Station, TX, USA). We performed Chi^2 test for dichotomous variables. Yates correction were used when expected numbers were ranged from 2.5 to 5 or Fisher exact test when expected numbers were lower than 2.5. Significance level was considered at 0.05. The mapping was managed by the software QGIS 2.14.

3. Results

3.1 Studies characteristics

3.1.1 Bibliometric analyses

The systematic search yielded 1886 articles, 647 of which were excluded as duplicates. Of the remaining 1239 studies, a further 870 were excluded after title reading and 178 were excluded after abstract reading. Further 87 studies were excluded, due to the fact that the articles were not original studies (25 articles) or there was no botanical identification (25 studies). All the motives of exclusion were presented in the flow-chart (Figure 1). In the remaining 104 studies, the use of herbal remedies was assessed. Two additional studies were included from the manual search. In total, 106 articles published between 1982 and 2017 were analyzed (Figure 1).

The studies retrieved were:

Eighteen studies presented quantified data documenting the use of species to control epilepsy seizures. Most used indicators were the Use Value (55 use reports), the Relative Frequency (41 use reports) and the Fidelity level (33 use reports). The Use Value index was employed to calculate the citation of plants during interviews and corresponds to the sum of the total number of use citations by all informants for a given species, divided by the total number of informants. The Relative Frequency was the species frequency divided by the total of frequency values for all species. The Fidelity Level corresponded to the number of informants that reported a use of a plant species to treat a particular disease divided by the number of informants that used the plants as a medicine to treat any given disease (Andrade-Cetto et al., 2011). Semi structured questionnaires were used in 6 studies, structured questionnaire, focus-groups and field observations in 1 study each. Key informants were traditional healers (in 10 studies), elders and local people (4 studies each), native people (2 studies) and religious, head of the villages and patients for 1 study each.

Twenty-three studies reported the use of species to control epilepsy seizures, without quantified data. Semi structured questionnaires were reported in 5 studies, field observation in 4 studies, structured questionnaire in 2 cases, focus-groups and participatory rural appraisal in 1 study each. Key informants were traditional healers (in 20 studies), elders and local people (respectively 8 and 7 studies each), head of the villages (2), patients and religious for 1 study each.

Sixty nine studies reported pharmacological data, from which 51 used *in vivo* evaluation models, 7 *in vitro* animal models and 11 both *in vitro* and *in vivo* techniques.

Four papers described both the use of HM to treat epilepsy seizures (29 use reports) and assessed its pharmacological activity.

3.1.2 Use and evaluation reports

A total of 497 use reports of species were found, divided into 3 groups:

Three hundred seventy seven ethnopharmacological survey use reports, corresponding to 264 species.

In these articles, remedies used were studied in a given geographical or cultural environment. Among the surveys, we distinguished two levels of evidence surveys: low level of evidence's surveys (with only qualitative data: investigators noted the use report for each species) and high levels of

evidence's surveys (quantitative data were provided taking into account use convergence parameters using indicators).

One hundred and twenty *in vitro* and *in vivo* models evaluation reports corresponding to 107 species.

Twenty nine reports encompassed both ethnopharmacological and pharmacological studies corresponding to 29 species.

3.1.3 Geographical distribution

Fifty-eight articles originated from Africa, 35 articles from Asia and 18 articles from Latin America. Regarding the number of species cited: 209 use reports were found in Africa (15 countries), 66 use reports in Latin America (7 countries) and 222 use reports in Asia (8 countries). Most of the publications included were carried out in India (n=23 articles), Nigeria (n=16), South Africa (n=13), Cameroun and Brazil (n=8 each). Species were mainly recorded from India (196 different species), Tanzania (81 of which 78 are different species), Belize (30 of which 21 are different), South Africa (28 different species) and Nigeria (22 different species). The distribution of species use reports across the world is shown in Figure 2. Although most of the publications were either ethnopharmacological or epilepsy models studies, we noted that only one Central American country (Belize) accounted both ethnopharmacological studies and preclinical studies in equal proportion (15 reports from each). The repartition of ethnopharmacological studies and preclinical trials by continents is presented in Table 1.

3.2 Ethnopharmacological and pharmacological approaches

Based on our inclusion criteria, we identified two types of studies; ethnopharmacological surveys and preclinical *in vitro* or *in vivo* studies.

3.2.1 Ethnopharmacological studies

Eighteen ethnopharmacological surveys assessed the species use through quantitative indicators, which represents 114 use reports. It corresponds to articles with a high level of evidence. The most reported quantitative technique was the Use Value (UV) (27.1% of use reports), which is based on the number of uses mentioned by each informant for a given species and the total number of people interviewed. The UV indicates the species that are considered most important by a given population (Phillips et al., 2002). The second most important quantitative measure was Relative Frequency representing the number of traditional healers using plants out of the total number of traditional healers (20.2% of use reports). Latin America used more quantitative indicators than Asia and Africa in the studies as we can see in Table 2 ($p<0.001$).

In Africa, the key informants who were mostly consulted during the surveys were villagers (83.3%) while in Latin America and Asia, traditional healers were the first (85.7% and 55.1%). In Africa, the number of traditional healers interviewed was 6.7%. The difference on the repartition of key informants was significative ($p<0.001$).

Concerning the 377 species cited in ethnopharmacological studies, 75 use reports (19.9%) were related to species that also manage other diseases (except diseases of the central nervous system). Eighty-one (21.5%) use reports concerned species that have various ethnobotanical usages on the central nervous system such as anxiolytic, analgesic, hypnotic, sedative, anti-psychotic, depressive or anti-depressive activities. Besides, the majority of the use reports in ethnopharmacological studies (n=221, 58.6%) did not give information about other ethnobotanical uses.

3.2.2 Pharmacological studies

Among 149 evaluation reports of species (120 species evaluated on models and 29 evaluated on both models and ethno pharmacology methods) recorded for *in vitro* and *in vivo* models, 41 species were assessed on *in vitro* models, 91 on *in vivo* models and 17 were completely screened (both *in vitro* and *in vivo* models). Species have been assessed on several biological models of epilepsy (Figure 3 and Table 3). *In vivo* models were mainly used (81.6% of the total numbers of models). *In vitro* model mostly used was the cerebral cortex bond-test GABA-A, with 55.2% of use reports. *In vivo* model mostly applied was the injection of pentenyltetrazole (34.9%), followed by maximal electroshock seizures (19.8%) and strychnine (16.7%). In Latin America, *in vitro* studies were most common (60.0%) whereas in Asia and Africa, *in vivo* studies were more frequent (respectively 76.0 and 58.1%). Ethanolic extracts were mainly used for *in vitro* studies whereas *in vivo* studies used aqueous, ethanolic, organic extracts (ether or dichloromethane extracts), or both types. Extracts were administered by intra-peritoneal route for 67.0% and other administrations were performed by oral route. More than 66.7% of preclinical trials did not involve toxicity studies and 21 studies (30.4%) did not use any positive control (AEDs) to compare efficacy with plant extracts. Only 20 studies (29.0%) could be considered as high quality studies respecting criteria described in the Guidelines for submission in peer-reviewed pharmacological literature (Mullane, Enna, Piette, & Williams, 2015).

3.3 Herbal remedies information

3.3.1 Botanical information

Three hundred fifty-one species belonging to 106 botanical families were reported. Families most cited were Leguminosae (n=38 species quoted), Compositae (n=37), Lamiaceae (n=28), Euphorbiaceae and Apocynaceae (n=21), and Araceae and Rutaceae (n=16). Botanical genera most represented were *Acorus* (n=14), *Bacopa* (n=10) followed by *Adiantum*, *Calotropis* (n=8), *Artemisia* and *Piper* (n=7). Data from ethnopharmacological surveys are presented in Table 4 and Table 5.

The species most cited was *Acorus calamus* L. (12 use reports and 2 evaluation reports), mentioned both in surveys and in biological assays (pentenyltetrazole (PTZ) and maximal electroshock (MES) models). *Bacopa monnieri* (L.) Wettst. was cited 8 times in four ethnopharmacological surveys and in 2 *in vivo* assays (extracts provided EEG protection as diazepam). *Leonotis leonurus* (L.) R.Br. (4 evaluation reports), *Uncaria Rhynchophylla* (Miq.) Miq. ex Havil., *Calotropis gigantea* (L.) Dryand. (3 evaluation reports each) had the greatest number of preclinical evaluation. *Ricinus communis* L., *Asparagus racemosus* Willd. and *Rauvolfia serpentina* (L.) Benth. ex Kurz were mentioned five times in total (4 use reports and 1 evaluation report).

3.3.2 Medicinal species use

Parts of species used were mainly leaves in Africa (39.2%) and Latin America (51.2%). In Asia, roots were mainly used (24.1%) and we also observed in this continent a great number of others parts as fruits, rhizomes, bulbs, flowers, seeds and resins. There was a significant difference for the repartition of species parts by continents as shown in Table 6 ($p<0.001$). For the mode of preparation, we noted decoction was mainly used in Africa (54.7%) and Latin America (38.2%). In Asia, the use of dry powders (22.6%) was the most common, followed by decoction (20.5%). We observed a wider variety of preparation modes in Asia with also an important proportion of healers who made maceration, extraction and paste. Other modes of preparation mentioned were juice, maceration, extraction and smoke. The distribution of the preparation modes was significantly

368 different between continents (p<0.001). The treatment was mainly administered by oral route for
369 the three continents but there was a significant difference (p=0.0128): in Asia, oral route was
370 preferred whereas in Latin America and Africa were reported various types of administration such as
371 topic administration, bath or inhalation. The treatment was prescribed daily for 100.0 % of surveys in
372 Africa and Asia, whereas 20% of species were administered once a month in Latin America.

373 ### 3.3.3 Effects of herbal remedies

374 The evaluation of the species on preclinical models showed a positive result for 129 species
375 evaluation reports, with different types of effects and action mechanisms identified (Table 7). In
376 total, 87 species evaluation reports demonstrated an activity; the best results were observed in
377 Africa where 70.3% of the species studied had their mechanism of action identified. Species acting at
378 the GABA A receptor with the greater effect by decreasing order were *Arctopus echinatus* L.,
379 *Cotyledon orbiculata* L., *Artemisia afra* Jacq. ex Willd*., Dioscorea dregeana* (Kunth) T.Durand & Schinz
380 and *Acacia sieberiana* DC*.. Tetrapleura tetraptera* (Schum. & Thonn.) Taub. presented a significant
381 dose dependent effect on latency, protection to control seizures and a high therapeutic index.
382 *Kalanchoe crenata* (Andrews) Haw., *Telfairia occidentalis* Hook.f. and *Gardenia resinifera* Roth
383 showed a significant effect on duration and latency of seizures. Species of Piperaceae family, *Piper*
384 *amalago* L. and *Piper tuerckheimii* C.DC., had an action inhibiting GABA transaminase, which reduce
385 significantly the frequency of seizures. An Ayurvedic formula with *Saussurea costus* (Falc.) Lipsch.,
386 *Cyperus rotundus* L. and *Bacopa monnieri* (L.) Wettst. provided a good protection on chronic seizures
387 (equally effective than diazepam) and recuperation of a normal neurologic function visible on the
388 EEG after 3 months with PTZ model.

389 Overall, 98 evaluation reports of mechanism of action were noted. Species acted mostly on the
390 GABAergic system (58 on 98 evaluation reports), as a GABA transaminase inhibitor or increasing the
391 aperture of chlorine channels on the benzodiazepine GABA A receptor. Eleven out of 98 evaluation
392 reports recorded an effect on the NMDA receptor, 10 on the glycine receptors and 8 on the sodium
393 channel receptors. Other mechanisms of actions involved were the reduction of peroxided lipids
394 (participating in oxidative damages) (4 evaluation reports), AMPA receptor binding (2 evaluation
395 reports), enhancement of the serotoninergic transmission, alteration of the Na^+/K^+ and Ca^{2+} ATP-ase,
396 reduction of the rate of prostaglandin in the limbic system, increase of anti-oxidant components and
397 inhibition of calcic T channel (1 evaluation report each). Six species had active constituents reported;
398 in Bum et al. (1996), *Cyperus articulatus* L. was reported to have rhizome constituents acting as
399 NMDA receptor antagonists at the NMDA recognition site and the glycine allosteric modulator site.
400 *Kalanchoe crenata* (Andrews) Haw. is known to have an endogenous compound (bufadienolide)
401 increasing GABA concentrations whereas *Marsilea quadrifolia* L. has its active constituent, marsilin,
402 acting by increasing the serotonin concentration in the brain*.* Several compounds in *Laurus nobilis* L*.,*
403 *Caesalpinia bonduc* (L.) Roxb. and *Origanum majorana* L. were reported having an activity on GABA-
404 ergic transmission.

405 ## 4. Discussion

406 ### *4.1 Strengths and limitations*

407 This systematic review aimed to report systematically the use of TCM in the control of epilepsy
408 seizures. In these studies, the diagnosis of epilepsy is often based upon the occurrence of generalized

409 tonic-clonic seizures, most of the time without a definite and precise diagnosis of the disease.
410 Indeed, the terms "epilepsy" or “epilepsy seizures” were used without any element referring to the
411 definition of the International League Against Epilepsy. Other types of seizures (especially focal
412 seizures or non-convulsive seizures such as absences) are even more difficult to identify, especially in
413 countries where there is a lack of knowledge in the diagnosis of epilepsy (Hounsossou et al., 2015;
414 Tran et al., 2007). Classifying epilepsy into focal and generalized has therapeutic implications:
415 generalized epilepsy responds better to treatment. Treatment failure in generalized epilepsy could
416 result from misclassification of epilepsy type and an initial inappropriate choice of antiepileptic
417 drugs. In addition, to consider the patient’s medical history and to conduct a clinical examination,
418 complementary exams such as EEG and brain imaging could be helpful to classify epilepsy as focal or
419 generalized, which was not done in the majority of studies that we have reported (Kumar et al.,
420 2017).

421 We considered both ethnopharmacological and preclinical trials evidence; that has not been done in
422 the previous meta-analyses or systematic reviews in this field. Even though this search strategy was
423 comprehensive, we have not weighted studies according to the level of evidence. Thus, a selection
424 (language and publication) bias cannot be excluded entirely. Second, the validity level of the
425 methodologies of the included publications was also not certain. Much of the risk of bias was
426 attributed to inadequate reporting in literature, considered including provision of insufficient
427 information on methodology of diagnosis of epilepsy, sampling, type of analysis and primary and
428 secondary endpoints. Moreover, there is insufficient evidence of effectiveness to support the use of
429 single herb recipes, to the extent that herbal medicine was consumed in association for the
430 management of epilepsy seizures.

431 Ambiguities and errors in the botanical nomenclature (no citation of author(s) of the names of plants,
432 misspelled names) and use (inaccurate voucher details, no details how specimens were identified)
433 could be observed in papers. We followed the key steps proposed to solve these taxonomic errors:
434 we verified names using The Plant List – a website attempting to bring all plant names together and
435 to impose a single coherent classification – in order to check synonyms and non-standard names.
436 After that, we copied and pasted standardized names from The Plant List into the main text, tables
437 and figures where required. Nevertheless, some of the errors would be tractable by checks on names
438 and others require a clearer policy to implement how specimens and names ((Rivera et al., 2014).
439 Regarding voucher specimens, we checked the main criteria to be cited within a paper – locality
440 where the sample was collected, collector’s name, collector’s unique collection number, herbarium
441 in which each specimen was deposited – and also criteria regarding their identification –
442 identification keys, floras, field manuals or other reference resources – and finally the botanical
443 authority indications (name of the expert and date of determination).

444 For preclinical trials, more randomized controlled trials examining safety and pharmacological effects
445 of herbal medicine for epilepsy seizures are required because only 29.0% of the studies used both
446 control groups and toxicity studies for the pharmacological evaluation. Moreover, the high
447 percentage of articles on the use of HM without quantified data could raise the interest of national
448 medicinal plant policies makers of the different countries. Indeed, it is essential to implement
449 credibility, relevance and sustainability of the research process by validating methodologies and
450 reagents in data generation.

4.2 Distribution of the studies

This systematic review examined the evidence for the pharmacological effects of herbal medicine in the management of epilepsy seizures. The review identified 106 studies, involving a total of 351 plant species.

The majority of data (75.9%) were provided by ethnopharmacological surveys, easier to set up than preclinical studies. These last studies require laboratory materials and appropriate conditions which may be difficult to meet in tropical and sub-tropical areas most often belonging to low-and-middle income countries (Fleming et al., 2017). The methodology used between studies is heterogeneously distributed leading to a loss of comparability between studies with a high and a low level of evidence. We encountered less use or evaluation reports in Latin America (66 reports) than in Asia or Africa (more than 200 reports each). This smaller number of reports in Latin America is probably due to the fact that in Africa and Asia, pharmacopeia of traditional medicine is included in the health care system (e.g. Traditional Chinese Medicine, African associations of traditional healers) whereas it is less common in Latin America (Bochaton, 2015; “WHO | WHO traditional medicine strategy”). Considering prevalence of epilepsy in the countries where we found studies (Table 8), we did not observe that the countries with the highest prevalence (Cameroon, Ethiopia, Panama) were not those with the greater use of medicinal plants (India, Tanzania, Belize).

In the same way, we observed more *in vivo* preclinical trials in Africa and Asia (58.1 and 60.0% respectively) while in Latin America *in vitro* studies were encountered more frequently (60.0%), which suggests Latin America research on pharmacopeia is more recent. However, there was a greater quality of studies in Latin America because of a use of quantitative indicators (62.5% of use reports) two to three-time more compared to Africa and Asia (respectively 21.9 and 26.6%). Integration of traditional medicine in the health care system could encourage high evidence level studies.

4.3 Cultural beliefs related to epilepsy

Shorvon and Farmer (1988) gathered sociocultural studies in developing countries to report the perceived causes of epilepsy; supernatural beliefs (e.g. breaking of taboo, visiting dangerous places), environmental factors (e.g. climate, phases of the moon), physical ailments (e.g. malaria, bang on the head or other accidents) and psychological determinants (e.g. anger, guilt, anxiety) were mentioned in Africa (Nigeria, Kenya), Asia (India), and Latin America (Ecuador). The Latin American people distinguished different types of epileptic seizures; the great evil was described as "heartbeat" and "becoming cold". The symptoms of the little evil were "the vision that is darkening" and a "behavioral cessation". Finally, the "explosive madness" seemed to describe the complex partial crises. In many countries, the etiology of the disease was explained by mystical causes; it is the result of punishment of the gods or deceased ancestors (Burneo, 2003). In a study conducted in Peru, epilepsy was perceived as being caused by emotional problems (25% of cases), neurocysticercosis (18%), heredity and witchcraft for respectively 16 and 15% of persons with epilepsy (PWE) surveyed (Auditeau et al., 2018). More recently in Asia, a majority of PWE didn’t know the etiology of their disease (18% of use reports), followed by cranial traumatism (16%) and fever (14%). This wide variety of beliefs can be correlated with the high diversity of therapeutic remedies used, which are discussed in ethnobotanical considerations.

492 *4.4 Ethnobotanical considerations*

493 Most of the participants to the ethnopharmacological surveys were traditional healers in Asia and
494 Latin America while village chiefs were more often interviewed in Africa. Several explanations may be
495 provided; first, the methodology of selection of samples was not the same according to studies.
496 Indeed some studies used randomized samples (Mallik, Panda, & Padhy, 2012; J. Sharma, Gairola,
497 Gaur, Painuli, & Siddiqi, 2013) while other studies not. Moreover, in Africa, the village chiefs were
498 educators about culture, counsellors, mediators, spiritual protectors and often traditional healers at
499 the same time (Zuma, Wight, Rochat, & Moshabela, 2016). At last, traditional healers in Africa were
500 probably more reluctant to answer this type of surveys. Interestingly, a study in East Africa showed,
501 when it came to gathering subjects, researchers were rarely involved in the challenging work of
502 enticing villagers to participate, preferring to rely on chiefs (Graboyes, 2010).

503 In Africa, leaves and roots were mainly used in the same proportion (39.2 and 34.9 respectively) in
504 the form of decoction (54.7%) whereas in Latin America leaves (51.2%) and other parts of species
505 (fruits, stems, rhizomes, bulbs, flowers, and seeds for 34.1%) were consumed in the form of
506 decoction (38.2%), infusion (29.4%) and maceration (26.5%). This greater variability of use could
507 reflect a greater propensity for experimentation. In Asia, roots and other parts of species were
508 mainly employed (respectively 24.1 and 47.3%) in form of dry powder or decoction (22.6% and 20.5%
509 respectively), reflecting a propensity to use more "elaborate" remedies. Oral route was mainly
510 employed in the three continents, but more in Asia (p=0.0128). Differences on part of species and
511 mode of preparation between continents could be explained by cultural differences (Chon, Heo,
512 Park, Kim, & Gorinstein, 2009).

513 *4.5 Ethnopharmacological discussion*

514 The following discussion deals with species ranked in descending order of use first (*Acorus calamus* L.
515 and *Bacopa monnieri* (L.) Wettst.) and then evaluation reports (*Leonotis leonurus* (L.) R.Br*., Uncaria*
516 *rhynchophylla* (Miq.) Miq. ex Havil. and *Calotropis gigantea* (L.) Dryand.). If we combine the results of
517 bibliometric analysis and evaluation studies, four others emergent species were the subject of both
518 ethnopharmacological and preclinical studies (*Ricinus communis* L*., Asparagus racemosus* Willd. and
519 *Rauvolfia serpentine* (L.) Benth. ex Kurz).

520 *Acorus calamus* L. (Acoraceae)

521 *Acorus calamus* L. is a cultivated herb native to Asia. Data from two ethnopharmacological studies
522 were collected and one study assessed *in vivo* anticonvulsant activity of the species. Two studies
523 reported other activities on the central nervous system (pain and headache treatment, anxiolytic
524 activity). Rhizomes were used in the care of epilepsy seizures in Indian communities (Rajput et al.,
525 2013; Sharma et al., 2004, 2012). Powder of rhizome, decoction and paste of rhizome were used,
526 depending on the region. In one region of India, Uttarakhand, it is mixed with *Selinum vaginatum* C.B.
527 Clarke and *Paeonia emodi* Royle powder and given at the rate of 1 half teaspoon twice a day.
528 Similarly, it can be mixed with leaves of *Ricinus communis* L. and *Caesalpinia mimosoides* Lam. in a
529 Kerala community. Oral route was employed in all cases in a daily treatment. Two quantitative
530 indicators, Use Value (UV) and Fidelity Level (FL), were mentioned. Questionnaires with 91 traditional
531 healers belonging to three indigenous communities, religious traditional healers, elderly people,
532 priests, housewives, villagers, village chief, Ayurvedic doctors, farmers and shepherd through
533 individual or focus-group interviews (J. Sharma et al., 2013; P. K. Sharma et al., 2004) were
534 performed for ethnopharmacological studies. In *in vivo* study, alcoholic extracts and essential oil

535 were assessed with pentenyltetrazole and maximal electroshock seizures. Methanolic extracts and
536 essential oil were protective against seizures but active constituents, α and β asarone, were
537 identified and presented toxic effects, including mutagenic and genotoxic effects. Although *Acorus*
538 *calamus* L. is the most cited species in our review, toxicity of α and β asarone limit its therapeutic
539 usage. Further researches are therefore needed to ensure the safety of this medicinal herb, and
540 "asarone free" varieties should be preferred for therapeutics as reported by Sharma et al., (2014).

541 *Bacopa monnieri* (L.) Wettst. (Plantaginaceae)
542 *Bacopa monnieri* (L.) Wettst. is an herbaceous, cultivated and pantropical species from the wetlands.
543 Data from four ethnopharmacological studies were collected and two studies assessed *in vivo*
544 anticonvulsant activity of the species. Two studies reported other activities on the central nervous
545 system (anti-psychotic activity and memory stimulant). Leaves were used in the care of epilepsy
546 seizures in 10 Indian communities (Poonam & Singh, 2009; Shanmugasundaram, Akbar, &
547 Shanmugasundaram, 1991; J. Sharma et al., 2013) and one Egyptian community of the Sinaï region
548 (Eissa et al., 2013). Decoction, juice and powder were used in India, depending on the region, while in
549 Egypt the infusion was consumed. Oral route was employed in all cases in a daily treatment.
550 Quantitative indicators, UV and FL, were mentioned three times. Semi-questionnaires with 700
551 informants (Eissa et al., 2013), surveys with traditional healers and local people (Poonam & Singh,
552 2009); and 91 traditional healers of 3 different communities (J. Sharma et al., 2013) were performed
553 for ethnopharmacological studies. In the 2 *in vivo* studies, ethanolic and aqueous leaves extracts
554 were assessed on pentenyltetrazole, pilocarpine, maximal electroshock seizures and strychnine acute
555 seizures-induced. Electrophysiological and neurological tests were also performed on a 3 month-
556 period. Extracts prevented the onset of seizures and provided EEG protection as effective as
557 diazepam. No toxicity studies were available in the papers reviewed. Overall, *Bacopa monnieri* (L.)
558 Wettst. presents beneficial effect on epilepsy associated behavioral deficits (especially memory and
559 cognitive enhancing effects), which suggest its role as adjuvant in the treatment of epilepsy seizures
560 and for managing side effects of AEDs (Mathew et al., 2010). Further researches should be
561 performed to elucidate its mechanism of action and confirm its role as adjuvant for epileptic
562 patients.

563 *Leonotis leonurus* (L.) R.Br. (Lamiaceae)
564 *Leonotis leonurus* (L.) R.Br. is a cultivated African herbaceous plant. Data from four pharmacological
565 studies were reported. One study reported other activity on headache.
566 Leaves, roots and bulbs were assessed in 3 *in vivo* studies (Bienvenu, Amabeoku, Eagles, Scott, &
567 Springfield, 2002; Fennell et al., 2004; Risa et al., 2004) and 2 *in vitro* studies (Risa et al., 2004).
568 Leaves fumigation were consumed in South Africa in order to treat epilepsy seizures. Ethanolic and
569 aqueous extracts were assessed on 4 models (PTZ, picrotoxine, bicuculline, NMDA) and a GABA
570 receptor binding test was performed on ethanolic extract. Diazepam and phenobarbitone were used
571 as controls. There is no binding to GABA-A receptor but certainly an indirect effect *via* the chlorine
572 channels which increase protection to control seizures and extend the latency of seizures in PTZ,
573 picrotoxine and NMDA models. No toxicity studies were available in the papers reviewed. Although
574 *Leonotis leonurus* (L.) R.Br. present interesting anticonvulsant activity, its psychoactive effects (also
575 known as cannabis-like effect) and its long-term toxicity indicate the health risk of this plant (Nsuala
576 et al., 2015). Further researches should be performed to assess the safety of this species.

577 *Uncaria rhynchophylla* (Miq.) Miq. ex Havil. (Rubiaceae)

578 *Uncaria rhynchophylla* (Miq.) Miq. ex Havil. is a wild Asian liana. We found data from three
579 pharmacological studies (C. L. Hsieh, Chen, et al., 1999; C. L. Hsieh, Tang, Chiang, Hsieh, & Lin, 1999;
580 C.-L. Hsieh et al., 2009; Lin & Hsieh, 2011). Alcoholic extracts were assessed on *in vitro* (measure of
581 the levels of lipid peroxide) and *in vivo* models (kaïnate, EEG and EMG recordings). Carbamazepine
582 was used as control. There is a concentration dependent effect on the decrease of peroxided lipids
583 (contribute to oxidative damage). The effect on protection against seizures and latency of seizures
584 was observed from 500 mg/kg. Decrease of the amplitude of action potential from pyramidal neuron
585 at the EEG, decrease neuronal death and modification of the expression of glial cells by a mechanism
586 involving glial proliferation were noticed. The protein implicated in the glial proliferation and which
587 had its level decreased with the extracts of *Uncaria rhynchophylla* (Miq.) Miq. ex Havil. was already
588 identified. No toxicity studies were available in the papers reviewed. Overall, a lack of
589 pharmacological and toxicological data regarding the use of *Uncaria rhynchophylla* (Miq.) Miq. ex
590 Havil. in the treatment of epilepsy seizures call for a better evaluation of this species (Ndagijimana et
591 al., 2013).
592
593 *Calotropis gigantea* (L.) Dryand. (Apocynaceae)
594 *Calotropis gigantea* (L.) Dryand. is a pantropical wild herbaceous species. Three pharmacological
595 studies and one ethnopharmacological study provided data (Kadiyala, Ponnusankar, & Elango, 2013;
596 J. Sharma et al., 2013). Infusion of flowers was used for the prevention of seizures in 3 different
597 communities of traditional healers of India. Leaves, crushed roots and stems of *Calotropis gigantea*
598 (L.) Dryand. were assessed in *in vivo* models of epilepsy (PTZ and MES). Phenytoin was used as
599 control. Decrease of the number, duration of seizures and increase of the latency of seizures were
600 observed. No toxicity was observed with the doses used in the study. Overall, *Calotropis gigantea* (L.)
601 Dryand. presents *in vivo* evidence of anticonvulsant activity. However toxicological studies indicate
602 that some parts of plants (i.e., latex and fruits) are toxic (Kadiyala et al., 2013). Therefore, further
603 researches should focus on the sub-acute and chronic toxicity of the part of plants (i.e., flowers,
604 leaves, roots, stems) used to manage epilepsy seizures.

605 *Ricinus communis* L. (Euphorbiaceae)
606 *Ricinus communis* L. is a cultivated widespread herbaceous plant. Data from five
607 ethnopharmacological studies were collected and one study assessed *in vivo* anticonvulsant activity
608 of the species. One study reported other activities on the central nervous system (fever and
609 headache treatment).
610 Leaves were used in the care of epilepsy seizures in Indian communities (Purkayastha, Dutta, & Nath,
611 2007; J. Sharma et al., 2013) and Saharian communities (Hammiche & Maiza, 2006). Infusion of
612 leaves, decoction and powder were used, depending on the region. In one region of India, Kerala
613 community, leaves can be mixed with leaves of *Ricinus communis* L. and *Caesalpinia mimosoides*
614 Lam.. Oral route was employed in all cases in a daily treatment. Three quantitative indicators, UV, FL
615 and total number of use reports, were mentioned. Questionnaires with 60 people including 20
616 traditional healers, 5 village chiefs, 10 women, 25 elderly people (Purkayastha, Nath, & Islam, 2005);
617 as well as interviews of 91 traditional healers from 3 indigenous communities, formal interviews with
618 a randomized sample and a follow-up (J. Sharma et al., 2013); and finally interviews of traditional
619 healers (Hammiche & Maiza, 2006) were performed for ethnopharmacological studies. In *in vivo*
620 study, alcoholic extracts were assessed on pentenyltetrazole and maximal electroshock seizures.
621 Ethanolic extracts were protective against seizures. No toxicity studies were available in the papers

reviewed, but this species is known to contain the highly toxic ricin mostly found in the seed of *Ricinus communis* L.. Although seeds of *Ricinus communis* L. are not used for epilepsy treatment in the papers reviewed, another toxic compound (ricinine) have been identified from others part of the plants including leaves (Worbs et al., 2011). Moreover, this compound is known to elicit seizures and is used as a chemical model of convulsive seizure (Ferraz et al., 2000). Altogether, the presence of toxic compounds in this species should be taken into account before using this plant for traditional medicine, and further studies should be performed to evaluate the toxicity of leaves.

Asparagus racemosus Willd. (Asparagaceae)

Asparagus racemosus Willd. is a wild herbaceous widely distributed in pantropical regions. Data from four ethnopharmacological studies were collected and one study assessed both use reports by communities and *in vivo* anticonvulsant activity of the species. One study reported other activity on the central nervous system (inducing paralysis). Roots and rhizomes were used in the care of epilepsy seizures in three Indian communities (Mallik et al., 2012; J. Sharma et al., 2013; U. K. Sharma et al., 2012). Decoction of roots was used in one community, while in another village the dry powder and the juice were consumed. Oral route was employed in all cases. The powder and decoction were taken twice a day during one month. Five quantitative indicators, the UV, the FL, the relative frequency of use reports, the relative importance and the cultural index were mentioned. Surveys with 91 traditional healers of 3 different communities, formal interviews with local population and elder people (J. Sharma et al., 2013); as well as surveys with traditional healers, village chiefs, religious healers, PWE and housewives (Mallik et al., 2012); and semi-structured interviews with 84 informants (village chiefs, traditional healers, religious healers, farmers between 45 and 70) (U. K. Sharma et al., 2012) were performed for ethnopharmacological studies. In the *in vivo* study, methanolic and aqueous root extracts were assessed on pentenyltetrazole and maximal electroshock seizures. Extracts provided protection against seizures. No toxicity studies were available in the papers reviewed, and most of the toxicological studies performed on *Asparagus racemosus* Willd. proved the long-term safety of the species (Singh et al., 2016). Further studies should be carried out to better understand its mechanism of action in the treatment of epilepsy seizures.

Rauvolfia serpentina (L.) Benth. ex Kurz (Apocynaceae)

Rauvolfia serpentina (L.) Benth. ex Kurz is a tropical cultivated shrub. Data from four ethnopharmacological studies were collected and one study assessed both use reports by communities and *in vivo* anticonvulsant activity of the species. One study reported other activities on the central nervous system (nervous disorders, insomnia treatment and anti-venomous). Powder of roots were used in the care of epilepsy seizures in five Indian communities (Poonam & Singh, 2009; J. Sharma et al., 2013). Oral route was employed twice a day. Three quantitative indicators, UV, FL and percentage of use reports were mentioned. Questionnaires with 91 traditional healers, priests, women, farmers, elder people and inhabitants (Poonam & Singh, 2009); as well as observations and focus group with elder people, traditional healers and people who have knowledge about plants of 60 villages (J. Sharma et al., 2013) were performed for ethnopharmacological studies. In an *in vivo* study, aqueous extract was assessed on pentenyltetrazole and strychnine models. Extracts provided protection against seizures. No toxicity studies were available in the papers reviewed. *Rauvolfia serpentina* (L.) Benth. ex Kurz contains the famous active compound reserpine which was discovered from this species in 1952. Although it has been proven to possess anticonvulsant activity in humans,

the numerous side-effects of this compound reduced its use in the treatment of comorbidity of epilepsy (Dey and De, 2010).

The use convergence was not frequent; only 2 species were reported more than 10. This could be partly explained by the wide area studied and the difference of ecosystems between the countries. Interestingly, within the same study area (rural communities in Peru), we observed a high use convergence of some widespread plants as *Valeriana officinalis* L., *Myristica fragrans* Houtt. and *Melissa officinalis* L. (Auditeau et al., 2018). These plants, which are not endemic to Peru, could be used because of a real effectiveness was observed. In this context, it will be interesting to provide pharmacological evaluation of these species in order to, if a pharmacological activity is demonstrated, raise awareness and establish training activities for traditional healers which are more often the first local actors consulted in case of epilepsy (60.5% of PWE in Peru had already used herbal remedies for the care of epilepsy).

Moreover, we noted a particularly interesting use convergence for one species which was found in 3 different continents: *Cassia fistula* L.. Seeds of this species were used as decoction in Northern Peru, Tanzania and India. For this same species, it will be interesting to compare ecological factors such as environmental factors (humidity, temperature, light and nutrients) which could influence the characteristics of the species and the specificities (e.g. quantity and quality of active constituents).

683 *4.6 Pharmacological approaches*

684 HM refers to the use of species or species-derived materials for therapeutic purposes and has been
685 used by herbalists and indigenous communities to treat body disorders for centuries. Most of HM
686 preclinical data in epilepsy seizures control were obtained in poorly design predictive animals models
687 (seizures induced by chemical agents or electroshocks). Some evidence indicates that species such as
688 *Cannabis sativa* L. (Massot-Tarrús & McLachlan, 2016) and *Huperzia serrata* (Thunb.) Trevis.
689 (Gersner, Ekstein, Dhamne, Schachter, & Rotenberg, 2015) may assist in the management of epilepsy
690 by improving seizures latency and seizure protection, possibly via the interaction with GABA and
691 NMDA receptors. This suggests that the use of HM as a treatment for epilepsy is biologically
692 plausible.

693 Preclinical data investigating the effect of species on epilepsy were mainly obtained on *in vivo*
694 seizures models (81.6%) induced by chemical agents for 80.2% of use reports (pentenyltetrazole,
695 strychnine, picrotoxine, pilocarpine, isoniazide or bicuculline) or electroshocks (maximal electroshock
696 seizures) for 19.8% of use reports. These models act on the neurotransmitters system and the most
697 popular techniques were acting on the GABAergic system (59.2%), as a GABA transaminase inhibitor
698 or a GABA A receptor agonist or increasing the aperture of chlorine channels on the benzodiazepine
699 GABA A receptor (Nsour, Lau, & Wong, 2000). Nowadays, few models are predictive of human forms
700 of epilepsies; among them, we can mentioned the MTLE mouse model (Depaulis & Hamelin, 2015;
701 Duveau et al., 2016), which recapitulates most of the electrophysiological and histopathological
702 features of human temporal lobe epilepsy; the genetic absence epilepsy rat from Strasbourg (GAERS)
703 which is a model of generalized epilepsy similar to the absence epilepsy observed in human and the
704 neurocysticercosis rat model which is generated by the intracerebral injection of the *Taenia solium* in
705 rat, leading to convulsive seizures in some animal (Verastegui et al., 2015). These models represent
706 the forms of epilepsy investigated in the clinic for the development of new AEDs but in our study, we
707 did not find any species evaluated on this type of models.

708 We found more aqueous extracts used in *in vivo* studies, in order to respect traditional remedies
709 which used more aqueous preparations (49.5% for decoctions, infusions) than alcoholic preparations
710 (5.0% for macerations). On 149 use reports for preclinical studies, only 24.8% provided toxicity
711 studies and only one use report provided long-term safety with studies of genotoxicity and
712 mutagenicity.

713 In preclinical trials, researchers test species one by one and try to isolate a single molecule. However,
714 the common point between ethnopharmacological studies is that herbal remedies are not a single
715 plant species but a mixture of several species. Proposed pre-clinical trials do not reflect the reality of
716 the field and are based on methods similar to those used for anti-epileptic drugs (traditional
717 practices should be assessed differently). The relevance of using such models in the evaluation of
718 traditional medicines may be questionable (Bodeker et al., 2002).

719 One open-label interventional trial (Devinsky et al., 2016) was performed in order to establish
720 whether addition of cannabidiol to existing anti-epileptic regimens would be safe, tolerated, and
721 efficacious in children and young adults with treatment-resistant epilepsy. Results show the median
722 reduction in monthly motor seizures was 36.5%. Randomized controlled trials are warranted to
723 characterize the safety profile and true efficacy of cannabidiol.

5. Conclusion

The epilepsy is profoundly culturally and socially mediated, and traditional medicine is recognized as a pillar of epilepsy care because of its ability to consider behavioral, nutritional, psychological and social factors (Lee et al., 2005).

For that reason, integration of TMC in national healthcare systems, promotion of efficacy, quality, safety of traditional medicine and increase of availability and accessibility to epilepsy care, belong to WHO strategies for 2014-2023. Nowadays, there is insufficient evidence to conclude that species with the higher convergence use are beneficial to patients suffering from epilepsy. The included trials were of different methodological quality (preclinical trials data *versus* ethnopharmacological data), which makes comparison difficult.

In the present review article, amongst 351 species reported to possess anticonvulsant activity:

(a) No plants have been tested for anticonvulsant activity clinically,

(b) The preliminary anticonvulsant activity screening on crude extracts has been carried out on 107 plants. Such plants need to be explored with a view to isolate active constituents and their mode of actions,

(c) Chemical constituents responsible for anticonvulsant activity have been reported in 8 plants and

(d) The possible mechanism of action has been reported for 125 plants.

The WHO has placed a great deal of emphasis on the integration of the traditional practices in modern biomedicine. Considering our results, the importance of TCM in the case of epilepsy seizures should be assessed and recognized, as contribution for the drawing of health policies for a better care of PWE in the world. Indeed, identification of vegetal species and their screening on *in vivo* rodent models of epilepsy can lead to formulate strategic recommendations and to decide if it would be relevant or not to develop traditional phyto-medication, more personalized and with fewer side-effects. Moreover, TMC is not only based on the use of plants but also on the use of rituals and dietary restrictions that it would be interesting to explore. A better management of seizures and improvement of PWE's quality of life should reduce the stigma associated with epilepsy and information campaigns and strategic recommendations will be interesting to conduct with traditional healers and medical practitioners.

The identification of plant extracts with a high anti-epileptic potential will be further characterized by appropriate models of seizures (*in vivo* models of chronic seizures with a better predictability) using a wide-range of study protocols allowing the validation of anti-epileptic potential for new AEDs. Relevant extracts should be further analyzed to identify and characterize the active ingredients. After validation of the possibility to further protect the ingredients coming from the selected plants, the best active ingredients should be protected and patented in agreement with the biodiversity Nagoya's convention.

Finally, it will be interesting to provide new models of epileptogenesis, in particular to study epilepsy associated with parasites and inflammation (Nash et al., 2015), as neurocysticercosis, to understand forms of epilepsy that are often treated with traditional medicine.

762 ***Glossary***

763 AEDs: Anti-Epileptic Drugs
764 AMPA: Alpha-amino-3-hydroxy-5-Methyl-4-isoxazolePropionic Acid
765 GABA: Gamma-AminoButyric Acid
766 GAERS: Genetic Absence Epilepsy Rat from Strasbourg
767 HEK: Human Embryonic Kidney Cells
768 HM: Herbal Medicine
769 MES: Maximal Electroshock Seizure
770 MTLE: Mesial Temporal Lobe Epilepsy
771 NMDA: N-Methyl-D-Aspartate
772 PTZ: PentenylTetraZole
773 PWE: Persons With Epilepsy
774 TMC: Traditional and Complementary Medicine
775 UV: Use Value
776 WHO: World Health Organization
777
778 ***Authors' contribution***
779 EA conducted the study design, manuscript writing, data collection, analysis and interpretation. FC
780 collected the data, interpreted it and corrected the manuscript. GB provided data analysis, made
781 critical comments and approved the final submission. JL, JJ and MB interpreted the data and
782 corrected the manuscript. VR helped design the study and corrected the manuscript. PMP completed
783 the study design and corrected the manuscript. FB designed the study, analyzed the data and
784 corrected the manuscript. All authors read and approved the final version.
785
786 ***Conflict of interest***
787 We wish to confirm that there are no known conflicts of interest associated with this publication and
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789

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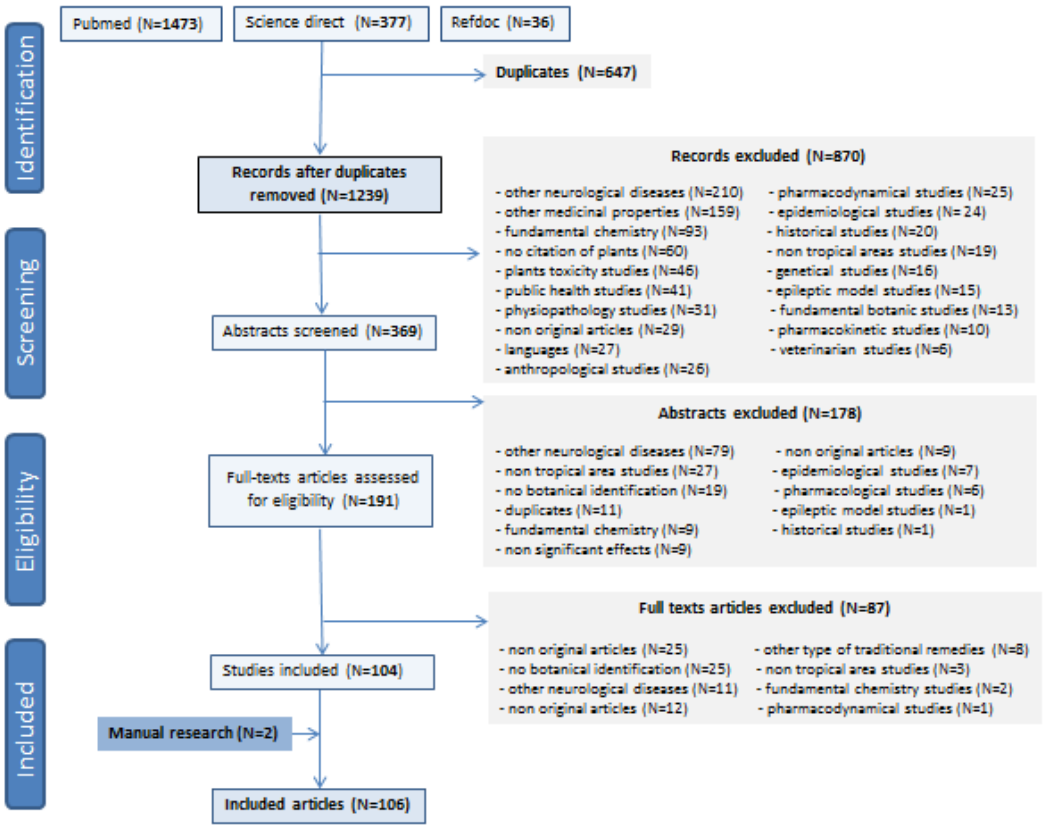

Figure 1: Flow-chart of the literature review

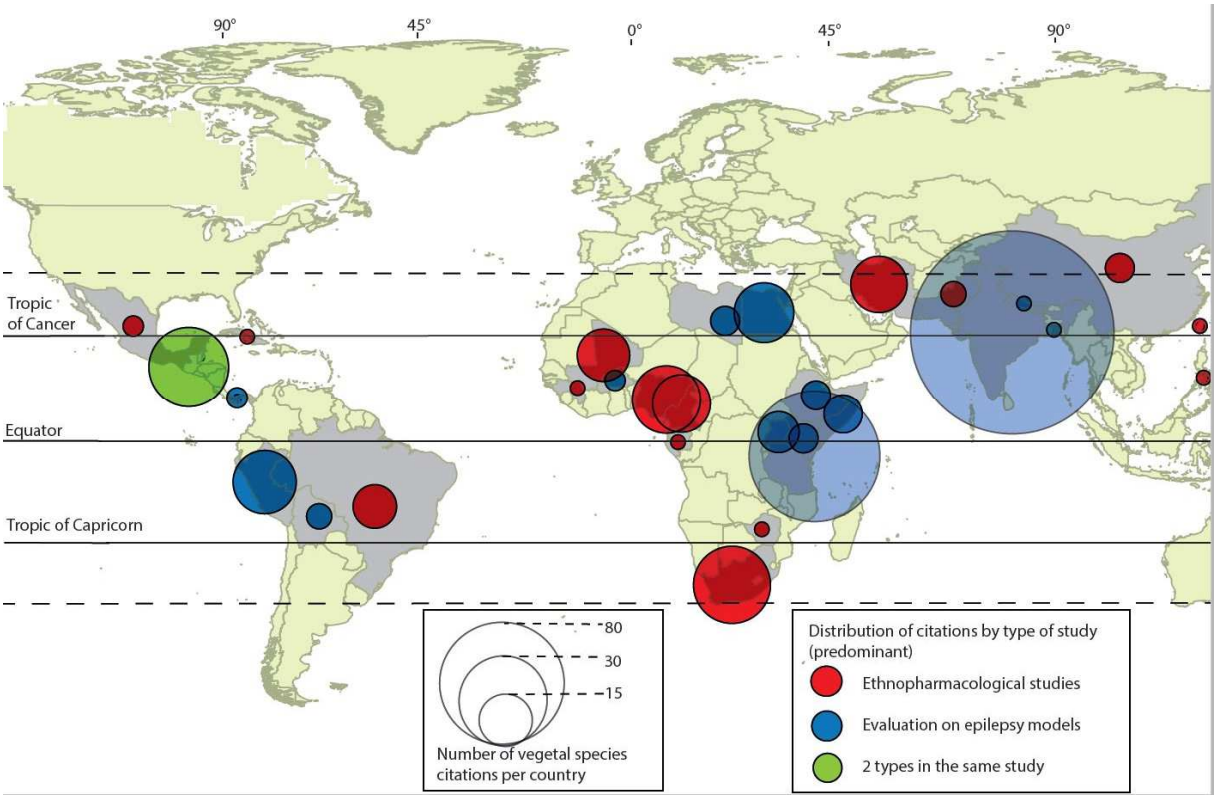

Figure 2: Distribution of plant species use reports by country and type of study

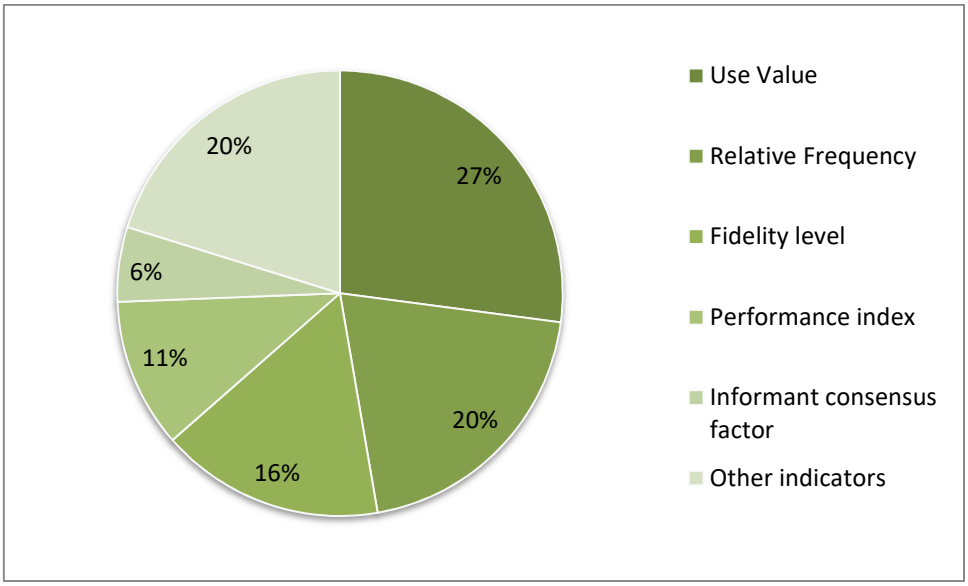

Figure 3: Repartition of quantitative indicators for ethnopharmacological studies

Table 1. Repartition of study type by continents

	Ethnopharmacological studies		Epilepsy models		
	Number	Frequency (%)	Number	Frequency (%)	p
Africa	137	64.9	74	35.1	0.005
Asia	184	78.6	50	21.4	
Latin America	56	69.1	25	30.9	
Total	377	71.7	149	28.3	

Table 2. Repartition of the quantification of the ethnopharmacological studies and key informants by continents

	Quantification			Key Informants			
	Number	Frequency (%)	p	Traditional healers	Other village members	Both	p
Africa	30	21.9		2	25	3	
Asia	49	26.6	<0.001	27	9	13	<0.001
Latin America	35	62.5		30	5	0	
Total	114	30.2		59	39	16	

Table 3. Preclinical models reported in the literature

Model	Number of use report	Percentage of use report
In vitro models		
Cerebral cortex bond-test GABA-A	32	55.2
Electrical potential recordings	10	17.2
Cerebral cortex bond-test NMDA, AMPA, glycine	6	10.3
Others	10	17.2
TOTAL	**58**	**100.0**
In vivo models		
PTZ	90	34.9
MES	51	19.8
Strychnine	43	16.7
Picrotoxine	20	7.8
Pilocarpine	18	7.0
Isoniazide	17	6.6
Bicuculline	8	3.1
Autres	11	4.3
TOTAL	**258**	**100.0**

AMPA: acide alpha-amino-3-hydroxy-5-méthyl-4-isoxazolepropionique, GABA: Gamma-AminoButyric Acid, MES: maximal electroshock seizure, NMDA: N-Methyl-D-Aspartate, PTZ: pentenyltetrazole

Table 4. Species most mentioned in the ethnopharmacological surveys without quantification

Species	Family	Coun-tries	Part of specie	Traditional preparation way	Adminis-tration	Doses	Informants	Sample size	Type of survey	Study period	Results	Reference
Carissa spinarum L.	Apocynaceae	Kenya	Roots	Decoction	PO	-	Local population, older people who have knowledge, traditional healers	-	Semi-structured interviews	March 2004 to February 2006	Ethnopharmacological use on epilepsy	Jeruto et al., 2008
Culcasia falcifoli Engl.	Araceae		Leaves	Ash								
Ehretia cymosa Thonn.	Boraginaceae		Leaves and root	Infusion								
Solanecio mannii (Hook.f.) C.Jeffrey	Asteraceae		Roots	Decoction								
Achyranthes aspera L.	Amaranthaceae	India	Whole plant	Pulverization	PO	1 s 2/day	Local populations, traditional practitioners in 4 tribes	-	Questionnaires and participatory rural appraisal (PRA)= Participatory rural evaluation	-	*Achyranthes aspera:* Plant with very good effectiveness in epilepsy for 2 tribes, moderate effectiveness in another tribe and not known in this indication either by one tribe *Evolvulus alsinoides:* Plant with a very good effectiveness in epilepsy for the 4 tribes, not known in this indication by traditional practitioners	Kumar et al., 2004
Evolvulus alsinoides (L.) L.	Convolvulaceae		Whole plant	Paste		1/day during 1 month						
Euphorbia dracunculoides Lam.	Euphorbiaceae	India	Leaves	Pulverization	PO	-	Traditional practitioners who apply Ayurvedic medicine, indigenous women, seniors	-	Questionnaires, consultations and interviews	September 2007 to July 2008	Traditional medicine use in India	Sharma et al., 2010
Gomphrena celosioides Mart.	Amaranthaceae		Leaves	Juice								
Ocimum gratissimum L.	Polygalaceae		Leaves	Paste								
Oxalis corniculata L.	Oxalidaceae		Leaves	Pulverization								

Species	Family	Coun-tries	Part of specie	Traditional preparation way	Adminis-tration	Doses	Informants	Sample size	Type of survey	Study period	Results	Reference
Allium cepa L.	Amaryllidaceae	India	Bulb	Extraction	PO	1 week	Traditional practitioners who apply Ayurvedic medicine (aged 35 to 80)	45	Semi-structured questionnaire with randomized survey	2005 to 2006	Traditional medicine use in India	Semwal et al., 2010
Aristolochia indica L.	Aristolochiaceae	India	Roots	Juice	In the nose	-	Traditional healers	-	-	-	Traditional medicine use in India	Pushpangadan et al., 1984
Ipomoea eriocarpa R. Br.	Convolvulaceae		Whole plant	Extraction	With honey							
Glycosmis pentaphylla (Retz.) DC.	Rutaceae		Whole plant	Juice	PO or on the head							
Euphorbia tirucalli L.	Euphorbiaceae	Somalia	Aerial parts	-	-	-	Traditional healers	-	-	-	Traditional medicine use in Somalia	Samuelsson et al., 1992
Jatropha curcas L.	Euphorbiaceae		Roots	-	-							
Flueggea virosa (Roxb. ex Willd.) Royle	Phyllanthaceae		Leaves	Juice	PO							
Launaea cornuta (Hochst. ex Oliv. & Hiern) C.Jeffrey	Compositae		Leaves and roots	Decoction	-							
Cullen corylifolium (L.) Medik.	Compositae	Somalia	Aerial parts	Paste	On the body and one drop in the navel	-	Traditional healers	-	-	-	Traditional medicine use in Somalia	Samuelsson et al., 1992
Dichrostachys cinérea (L.) Wight & Arn.	Mimosaceae		-	Decoction								
Indigofera tinctoria L.	Leguminosae		Leaves	Juice and decoction								
Baccharoides lasiopus (O.Hoffm.) H.Rob.	Compositae	Tanzania	Leaves	Decoction	-	-	Traditional healers	114	-	November to December 1978 and 1979	Traditional medicine use in Tanzania for children (*Conyza pyrrhopappa, Markhamia obtusifolia, Senna singueana,*	Hedberg et al., 1982
Conyza pyrrhopappa Sch.Bip. ex A.Rich	Compositae		Roots	Decoction	-							
Gymnanthemum coloratum (Willd.) H.Rob. & B.Kahn	Compositae		Leaves and inflorescence	Infusion	Inhalation							
Gymnosporia heterophylla (Eckl. &	Celastraceae		Roots	Decoction	PO							

Zeyh.) Loes.											*Uvaria acuminate)* and adults for other plants	
Launaea cornuta (Hochst. ex Oliv. & Hiern) C.Jeffrey	Compositae		Roots and leaves	Decoction	-							
Markhamia obtusifolia (Baker) Sprague	Celastraceae		Roots	Paste	-							
Microglossa pyrifolia (Lam.) Kuntze	Compositae		Roots and whole plant	Decoction	-							
Psiadia punctulata (DC.) Vatke	Compositae		Roots and leaves	Pulverization	On the tongue							
Senna singueana (Delile) Lock	Cesalpinaceae		Roots	Decoction	-							
Uvaria acuminata Oliv.	Annonaceae		Roots	Decoction	PO							
Uvaria leptocladon Oliv.	Annonaceae		Roots and leaves	Decoction	-							
Vernonia hochstetteri Sch.Bip. ex Walp.	Compositae		Whole plant	Decoction	-							

Species	Family	Coun - tries	Part of specie	Traditional preparation way	Adminis- tration	Dose	Informants	Sample size	Type of survey	Study period	Results	Reference
Catunaregam nilotica (Stapf) Tirveng.	Rubiaceae	Tanzania	Roots and bark of roots	Decoction and pulverization	Inhalation of powder	-	Traditional healers	114	-	November to December 1978 and 1979	Traditional medicine use in Tanzania for children (*Hoslundia opposita, Grewia forbesii* and *Waltheria indica)* and adults for other plants	Hedberg et al., 1983
Crossopteryx febrifuga (Afzel. ex G.Don) Benth.	Rubiaceae		Leaves and bark of roots	Pulverization and juice	-							
Grewia forbesii Harv. ex Mast.	Tiliaceae		Roots	Decoction	-							
Solanum incanum L.	Solanaceae		Fruit	Paste	-							
Waltheria indica L.	Malvaceae		Leaves and roots	Decoction	Inhalation and PO							
Dichrostachys cinerea (L.) Wight & Arn.	Mimosaceae		-	Decoction	-							
Flueggea virosa (Roxb. ex Willd.) Royle	Phyllanthaceae		Leaves	Juice	PO							
Hoslundia opposita Vahl	Lamiaceae		Roots	Decoction	-							
Curculigo orchioides Gaertn.	Amaryllidaceae	India	Roots	Paste	-	-	Local and community elders	-	-	1998 to 2001	Traditional medicine use in India	Singh et al., 2002
Evolvulus alsinoides (L.) L.	Convolvulaceae		Leaves	Paste								
Justicia ephemera Leonard	Acanthaceae	Panama	Whole plant	-	On chest and arms	-	Native informants with traditional healers help, Traditional healers	-	-	-	Traditional medicine use in Panama for children (*Justicia ephemera)* Traditional medicine use in Panama and Egypt too (*Sapindus saponaria)*	Gupta et al., 1993
Sapindus saponaria L.	Sapindaceae		-	Infusion	-							
Sesbania grandiflora (L.) Pers.	Leguminosae	Bangladesh	Fresh leaves	Juice with *piper nigrum*	PO	4 s 2/day during 15-20 days	Traditional healers in 2 villages	-	Semi-structured questionnaires and guided field walking	-	Traditional medicine use in Bangladesh	Rahmatullah et al., 2012
Capparis tomentosa Lam.	Capparidaceae	Ethiopia	Roots	-	Around the neck	-	Traditional practitioners and farmers over 25	38	Individual interviews	2003 to 2004	Specific traditional medicine use for epilepsy in Ethiopia	Giday et al., 2007

Species	Family	Coun-tries	Part of specie	Traditional preparation way	Adminis-tration	Doses	Informants	Sample size	Type of survey	Study period	Results	Reference
Artemisia nilagirica (C.B.Clarke) Pamp.	Compositae	India	Leaves	Infusion	-	-	Elders, traditional healers	-	-	2000 to 2002	Traditional medicine use in India	Sharma et al., 2004
Acorus calamus L.	Araceae		-	-								
Cannabis sativa L.	Cannabinaceae		-	-								
Cissampelos pareira L.	Menispermaceae		-	-								
Nardostachys jatamansi (D.Don) DC.	Valerianaceae		Roots	-								
Helichrysum setosum Harv.	Compositae	Tanzania	Leaves	Decoction	PO	-	Traditional healers	-	-	-	Traditional medicine use in Tanzania	Chhabra et al., 1984
Uvaria leptocladon Oliv.	Annonaceae		Leaves and young growths	Decoction	-							

Species	Family	Coun-tries	Part of specie	Traditional preparation way	Adminis-tration	Doses	Informants	Sample size	Type of survey	Study period	Results	Reference
Abrus precatorius L.	Leguminosae	Tanzania	Leaves	Infusion	PO	3 s 2/day	Traditional healers	100	Structured questionnaires with definition of the epilepsy required	2001	Traditional medicine use in Tanzania, specific for epilepsy	Moshi et al., 2005
Abrus shimperi Baker	Leguminosae		Leaves	Infusion	PO	1 half cup 3/day						
Acacia asak (Forssk.) Willd.	Leguminosae		Bark of stem	Decoction	Inhalation	-						
Acalypha ornata Hochst. ex A.Rich	Euphorbiaceae		Roots	Decoction	PO	2/day						
Adhatoda engleriana (Lindau) C.B.Clarke	Acanthaceae		Roots	Paste	PO	3 s 3/day						
Afzelia quanzensis Welw.	Leguminosae		Seeds	Maceration	Topic	-						
Ageratum conyzoides (L.) L.	Compositae		Leaves, roots	Decoction	PO	3 s 3/day						
Albizia anthelmintica Brongn.	Mimosaceae		Bark of stem	Decoction	PO	1 cup 3/day						
Albizia petersiana (Bolle) Oliv.	Mimosaceae		Roots	Decoction	PO	a quarter 3/day						
Antidesma venosum E.Mey. ex Tul.	Euphorbiaceae		Leaves, bark of stem	Decoction	PO	3 s 2/day						
Apodytes dimidiata E.Mey. ex Arn.	Icacinaceae		Roots, bark of stem	Decoction	PO	1 cup 2/day						
Arctotheca caléndula (L.) Levyns	Compositae		Roots	Decoction	PO	1 cup 3/day						
Aristolochia parensis Engl. & Peter	Aristolochiaceae		Roots	Decoction	PO	1 s 2/day						
Cadaba kirkii Oliv.	Capparidaceae		Leaves	Decoction	PO	1 half cup 2/day						
Cassia fistula L.	Leguminosae		Bark of stem	Paste	PO	2/day						
Cassine schelechteriana Loes.	Celastraceae		Roots	Decoction	PO	a quarter 2/day						
Catunaregam obovata (Hochst.) A.E.Gonç.	Rubiaceae		Bark of stem	Decoction	PO	1 half cup 2/day						
Chrysanthemoides monilifera (L.) Norl.	Compositae		Leaves	Decoction	PO	1 cup 2/day						
Cissus quadrangularis L.	Vitaceae		Leaves, roots	Decoction	PO	2 s 3/day						
Clausena anisata (Willd.)	Rutaceae		Roots, bark	Decoction	Inhalation	-						

Hook.f. ex Benth.			of stem									
Commiphora africana (A.Rich.) Endl.	Burseceae		Leaves	Decoction	PO	3 s 2/day						
Curcuma longa L.	Zingiberaceae		Leaves	Decoction	PO	1 cup 3/day and 1 inhalation						
Cussonia spicata Thunb.	Araliaceae		Roots	Decoction	Inhalation	2 s 3/day						
Cussonia zimmermanni Harms	Araliaceae		Roots	Paste	PO	1 s 3/day						
Dioscorea preussii Pax	Dioscoreaceae		Roots	Decoction	PO	1 cup 3/day						
Dodonaea viscosa (L.) Jacq.	Sapindaceae		Roots	Decoction	PO	1 cup 3/day						
Ehretia amoena Klotzsch	Boraginaceae		Roots	Decoction	PO	1 cup 2/day						
Erythrophleum suaveolens (Guill. & Perr.) Brenan	Leguminosae		Leaves	Decoction	PO	a quarter 3/day						
Euclea natalensis A.DC.	Ebenaceae		Roots	Decoction	PO	2/day						
Fernandoa magnifica Seem.	Bignoniaceae		Bark of stem	Paste	Inhalation	3 s 2/day						
Ficus ingens (Miq.) Miq.	Moraceae		Bark	Decoction	PO	3 s 2/day						
Ficus sycomorus L.	Moraceae		Leaves	Decoction	PO	a quarter 3/day						
Grewia damine Gaertn.	Tiliaceae		Roots	Decoction	PO	1 half cup 3/day						
Harrisonia abyssinica Oliv.	Simaroubaceae		Leaves	Decoction	PO	2 s 2/day						
Hibiscus subdariffa Rottb.	Malvaceae		Bark of stem	Maceration	PO	1 cup 3/day						
Hoslundia opposita Vahl	Lamiaceae		Roots	Decoction	PO	3 s 2/day						
Keetia hispida (Benth.) Bridson	Rubiaceae		Roots	Decoction	PO	a quarter 2/day						
Lobelia anceps L.f.	Campanulaceae		Leaves	Decoction	PO	1 half cup 1/day						
Lonchocarpus capassa Rolfe	Leguminosae		Roots	Decoction	PO	-						
Morella salicifolia (Hochst. ex A. Rich.) Verdc. & Polhill	Myricaceae		Roots	Decoction	Inhalation	a quarter 3/day						
Ocimum gratissimum L.	Polygalace		Leaves	Paste	PO	2/day						

	ae											
Ophiuros exaltatus (L.) Kuntze	Poaceae		Roots	Pulverization	Topic	1-2/day						
Oplismenus hirtellus (L.) P.Beauv.	Poaceae		Leaves	Decoction	Topic	1 half cup 2/day						
Ozoroa insignis Delile	Anacardiaceae		Roots	Decoction	PO	1 cup 3/day						
Encephalartos hildebrandtii A.Braun & Bouc	Zamiaceae		Bark of stem	-	PO	-						
Rauvolfia mannii Stapf	Apocynaceae		Roots	Maceration	-	1 s 2/day						
Salacia stuhlmanniana Loes.	Celastraceae		Bark of stem	Pulverization, decoction	PO	2 s 3/day						
Maerua cylindricarpa Gilg & Gilg-Ben	Capparidaceae		Leaves	-	-	-						
Pouzolzia mixta Solms	Urticaceae		Roots	-	-	-						
Schlecheterina mitostemmatoides Harms	Passifloraceae		Bark of stem	-	-	-						
Uvaria leptocladon Oliv.	Annonaceae		Bark of stem	-	-	-						
Xylopia arenaria Engl.	Annonaceae		Roots	-	-	-						
Tamarindus indica L.	Leguminosae		Roots	Decoction	PO	1 cup 2/day						
Tephrosia aequilata Baker	Leguminosae		Bark of stem	Decoction, paste	PO	1 s 3/day						
Vepris nobilis (Delile) Mziray	Rutaceae		Roots	Decoction	PO	1 half cup 2/day						
Vitex monbassae Vatke	Verbenaceae		Roots	Pulverization	PO	1 s 3/day						
Warburgia stuhlmannii Engl.	Capparidaceae		Bark of stem	Decoction	PO	2 s 2/day						
Warburgia ugandensis Sprague	Capparidaceae		Bark of stem	Pulverization	PO	1 cup 2/day						
Zanthoxylum chalybeum Engl.	Rutaceae		Roots	Decoction	PO	3 s 3/day						

Species	Family	Coun-tries	Part of specie	Traditional preparation way	Adminis-tration	Dose s=	Informants	Sam-ple size	Type of survey	Study period	Results	Reference
Bactris gasipaes Kunth	Arecaceae	Peru	Leaves, thorns	Infusion	Bath	-	-	30	2 steps for data collection: 1) informants surveyed in different ecotypes with different plant collection: name, plant species, use and structured interviews 2) semi-structured interviews: regarding treatments, diagnosis, therapeutic strategies	2006 to 2008	Traditional medicine use in Peru to treat "mal aire" (epileptic symptoms)	Valadeau et al., 2010
Costus productus Gleason ex Maas	Zingiberaceae		Leaves	Infusion	Bath	-						
Dichorisandra hexandra (Aubl.) Standl.	Commeliaceae		Flowers	Juice	Ocular instillation	one drop						
Elaphoglossum cuspidatum (Willd.) T. Moore	Lomariopsidaceae		Leaves	Infusion	Bath	-						
Elaphoglossum megalurum Mickel	Lomariopsidaceae		Leaves	Infusion	Bath	1/day						
Elaphoglossum raywaense (Jenman) Alston	Lomariopsidaceae		Leaves	Infusion	Bath	1/day						
Acacia amythethophylla A.Rich.	Leguminosae	Uganda	Roots	Pulverization	Inhalation, PO, topic	-	Traditional healers and heads of household	173	Semi-structured interviews, guided questionnaires, direct field observations of plant collection conducted by local research assistants (pilot study before)	June 2000 to June 2001	Traditional medicine use in Uganda	Tabuti et al., 2003
Acacia seyal Delile	Leguminosae		Roots	Pulverization	PO, bath, topic							
Carissa spinarum L.	Apocynaceae		Roots	Pulverization	PO, bath, topic							
Combretum collinum Fresen.	Combretaceae		Roots	Pulverization	PO, bath, topic							
Kalanchoe densiflora Rolfe	Crassulaceae		Leaves: sap	Extraction and infusion	PO, eye, navel instillation							
Oncoba spinosa Forssk.	Flacourtiaceae		Roots	Pulverization	PO, inhalation							
Terminalia glaucescens Planch. ex Benth.	Combretaceae		Roots	Pulverization	PO, bath, topic							
Asparagus racemosus Willd.	Asparagaceae	India	Roots	Extraction	PO	-	Village chiefs, traditional	-	Selection for interviews by randomization	2008 to 2011	Traditional medicine use in India	Mallik et al., 2012

Calotropis procera (Aiton) Dryand.	Asclepia daceae		Leaves	Juice	Navel instillation		healers, patients, religious, housewives					
Anastatica hierochuntica L.	Brassica ceae	Sahara	Whole plant	Decoction	PO	-	Traditional healers	-	-	2004	Traditional medicine use in Sahara	Hammiche et al., 2006
Calotropis procera (Aiton) Dryand.	Asclepia daceae		Leaves	Drying	Inhalation							
Citrullus colocynthis (L.) Schrad.	Cucurbita ceae		Fruit	Infusion	PO							
Ricinus communis L.	Euphorbi aceae		Seeds	Decoction	PO							
Yushania alpine (K.Schum.) W.C.Lin	Poaceae	Uganda	Roots	Bath	Topic	-	Key informants	36	-	-	Traditional medicine use in Uganda	Sucher et al., 2015

Species	Family	Coun-tries	Part of specie	Traditional preparation way	Adminis-tration	Doses	Informants	Sample size	Type of survey	Study period	Results	Reference
Euclea racemose L.	Ebenaceae	Ethiopia	Roots	Decoction	PO	Before the meal	-	-	Interviews, focus group, field collection, market research	-	Traditional medicine use in Ethiopia	Goel et al., 2015
Withania somnifera (L.) Dunal	Solanaceae		Roots	Decoction	PO							
Cascabela thevetia (L.) Lippold	Apocynaceae	Mexico	Seeds	Maceration	PO	1/month or if necessary	-	-	Interviews in markets, houses of traditional healers	2001 to 2006	Traditional medicine use in Peru	Alonso-Castro et al., 2017
Ambrosia peruviana Willd.	Compositae		Leaves, stem	Decoction	PO	-						
Lonicera japonica Thunb.	Caprifoliaceae		Whole plant	Decoction	PO	3-4 cup/day during 2-3 months						
Cassia fistula L.	Leguminosae		Seeds	Maceration	PO	1 cup/day during 15-20 days						
Myroxylon balsamum (L.) Harms	Leguminosae		Seeds	Juice	PO	3 little cup/day						
Tamarindus indica L.	Leguminosae		Fruit	Decoction	PO	1 glass/day during 30 days						
Aiouea dubia (Kunth) Mez	Lauraceae		Seeds	Decoction, bath	PO, bath	1/month						
Ocotea floribunda (Sw.) Mez	Lauraceae		Seeds, leaves, flowers	Decoction	PO	Decoction: 1L/day 7 to 15 days Limpia: 3 times a week						
Malva sylvestris L.	Malvaceae		Leaves, stem	Decoction	PO	1L/day during 15 days						
Myristica fragrans Houtt.	Myristicaceae		Seeds	Decoction	PO	1/month						
Peperomia inaequalifolia Ruiz & Pav.	Piperaceae		Whole plant	Inhalation	PO, inhalation	3-4/day during 1-2 months						
Laccopetalum giganteum (Wedd.) Ulbr.	Ranunculaceae		-	Decoction	PO	1-2 cup/day during 25 days						
Viola tricolor L.	Violaceae		Whole plant	Decoction	PO	3 cup/day						

PO: *per os*, s: spoon

Table 5. Species most mentioned in the ethnopharmacological surveys with quantitative indicators

Species	Family	Coun - tries	Part of specie	Traditional preparation way	Adminis-tration	Doses	Informants	Sample size	Type of survey	Quantifi-cation of use	Study period	Results	Referenc e
Acorus calamus L.	Araceae	India	Fresh rhizome	Paste	PO (for all the plants)	2/day	Traditional healers of 3 different communities	91	-	Use value (UV) and fidelity level (FL)	Between 2008 and 2012 at different seasons	UV : 0,11, FL : 16,67% UV : 0,31, FL : 47,83% UV : 0,23, FL : 44,44% UV : 0,41, FL : 45,83 UV : 0,2, FL : 25,93 UV : 0,14, FL : 20% UV : 0,34, FL : 43,48% UV : 0,24, FL : 25% UV : 0,33, FL : 39,13% UV : 0,3, FL : 32% UV : 0,31, FL : 47,37% UV : 0,17, FL : 21,43% Traditional medicine use in Bolivia	Sharma et al., 2013
Allium sativum L.	Amaryllidaceae		Bulb	Decoction		half-cup							
Asparagus racemosus Willd.	Asparagaceae		Roots	Powder		2g 2/day for 2-3 weeks							
Bacopa monnieri (L.) Wettst.	Plantaginaceae		Leaves	Paste, juice, decoction		2 or 3/day							
Boerhavia diffusa L.	Nyctaginaceae		Roots	Powder		3g							
Calotropis gigantea (L.) Dryand.	Apocynaceae		Bark	Decoction		1s 2/day for 2weeks							
Datura stramonium L.	Solanaceae		Fresh leaves and roots	Decoction		2/day							
Oxalis corniculata L.	Oxalidaceae		Whole plant	Decoction		2s							
Punica granatum L.	Punicaceae		Leaves	Decoction		half-cup							
Rauvolfia serpentina (L.) Benth. ex Kurz	Apocynaceae		Roots	Decoction		1g, 2/day							
Ricinus communis L.	Euphorbiaceae		Leaves	Infusion		-							
Vitex negundo L.	Verbenaceae		Roots	Powder		1-2s 1-2/day							
Dicerothamnus rhinocerotis (L.f.) Koek.	Compositae	South Africa	Leaves	Infusion	PO (for all the plants)	-	Women between 50 and 75 years old and men (people aged 45 to 65)	44	2 steps: 1) first basic questionnaire 2) specific	Percentage of citations and Use value	-	UV: 0.5 Percentage of citations: 47.5% UV: 1.4 Percentage of citations: 17.4% UV: 1.8	Thring et al., 2006
Dodonaea viscosa (L.) Jacq.	Sapindaceae		Leaves	Infusion		3/day							

Artemisia afra Jacq. ex Willd	Compositae		-	-		-			questionnaires			Percentage of citations: 75% UV: 1.7	
Ruta graveolens L.	Rutaceae		Leaves	Infusion		-						Percentage of citations: 72.5% Ethnopharmacological use as anti convulsant	

Species	Family	Coun - tries	Part of specie	Traditional preparation way	Adminis-tration	Doses	Informants	Samp le size	Type of survey	Quantifi-cation of use	Study period	Results	Reference
Artemisia vulgaris L.	Compo sitae	Bolivi a	Roots	Decoction	PO (for all the plants)	-	Families related to traditional farming activities (people aged 40 to 80)	56	-	Total number of citations and pertinent percentage of citations	January to June 2002	Total number of citations: 2 and pertinent percentage of citations: 3.57% Total number of citations: 4 and pertinent percentage of citations: 7.14 Total number of citations: 2 and pertinent percentage of citations: 3,57	Fernandez et al., 2003
Dianthus caryophyllus L.	Caryop hyllace ae		Flowers	Infusion									
Franseria artemisioides Willd.	Compo sitae		Roots	Infusion									
Bacopa monnieri (L.) Wettst.	Plantag inaceae	India	Leaves	Decoction	PO (for all the plants)	100-150 ml 2/day	Local users, people who know the plants, traditional practitioners (people aged 50 to 80)		-	Frequency of use by the community (properties considered valid if confirmed by at least 10 users and 5 healers)	January 2006 to Decembe r 2007	Frequencies of use : 41% 45% 41% 44% 29% 23% Traditional medicine use in India	Poonam et al., 2009
Curculigo orchioides Gaertn	Amaryll idaceae		Roots	Pulverization		2 s 2/day							
Cynodon dactylon (L.) Pers.	Poacea e		Whole plant	Infusion		50 ml 2/day							
Evolvulus Alsinoides (L.) L.	Convol vulacea e		Whole plant	Juice		2-3 s 2/day							
Plectranthus amboinicus (Lour.) Spreng.	Lamiac eae		Leaves	Juice		1 s 2/day							
Rauvolfia serpentina (L.) Benth. ex Kurz	Apocyn aceae		Roots	Pulverization		1-2 s 2/day							
Allium cepa L.	Amaryll idaceae	Nigeri a	Bulb	Pulverization	External on the face	-	Traditional practitioners, community of elders, patients (median age of 65 years)	930	-	Performance index (Ip: difference between % plant quotation for a given disease and % disease quotation)	August 2000 to Decembe r 2001	Ip = 1. Plant cited 87 times Ip = 2. Plant cited 140 times *Allium cepa* has a medium and *Jatropha curcas* a high traditional medicine use	Ajibesin et al., 2008
Jatropha curcas L.	Euphor biaceae		Leaves	Pulverization	PO								
Ricinus communis L.	Euphor biaceae	India	Leaves	Infusion	PO	-	Traditional healer, chiefs, women, elderly	60	-	Number total and percentage of citations	2001 to 2002	Number total of citations: 6 Percentage of citations: 10%	Purkayasth a et al., 2005

Species	Family	Coun-tries	Part of specie	Traditional preparation way	Admini s-tration	Dose	Infor mant s	Sample size	Type of survey	Quantifi-cation of use	Study period	Results	Reference
Anastatica hierochuntica L.	Brassicacea e	Egypt	Whole plant, fruit	Decoction	PO (for all the plants)	-	Men aged 49 to 69	700	Intervie ws with semi-structur ed questio nnaires	I/P (number of interview / number of inhabita nts) and UV	March 2006 to March 2011	I/P : 0,11 et UV : 0,27 I/P : 0,05 et UV : 0,8 I/P : 0,21 et UV : 0,14 I/P : 0,21 et UV : 0,19 I/P : 0,05 et UV : 0,6 I/P : 0,05 et UV : 0,8 I/P : 0,21 et UV : 0,24 I/P : 0,05 et UV : 0,8 I/P : 0,21 et UV : 0,09 I/P : 0,21 et UV : 0,19 I/P : 0,21 et UV : 0,09 I/P : 0,05 et UV : 0,8 I/P : 0,21 et UV : 0,09 I/P : 0,21 et UV : 0,33 I/P : 0,05 et UV : 0,2 I/P : 0,05 et UV : 0,4 I/P : 0,49 et UV : 0,1 Traditional medicine use in Egypt	Eissa et al., 2013
Bacopa monnieri (L.) Wettst.	Plantaginace ae		Aerial parts	Infusion									
Citrullus colocynthis (L.) Schrad.	Cucurbitace ae		Fruit	-									
Datura stramonium L.	Solanaceae		Aerial parts	Infusion									
Ferula sinaica Boiss.	Apiaceae		Roots	Maceration									
Globularia arabica Jaub. & Spach	Globulariace ae		Whole plant	Infusion									
Haplophyllum vermiculare Hand.-Mazz	Rutaceae		Leaves	Infusion									
Lavandula pubescens Decne	Lamiaceae		Flowers	Infusion									
Leontice leontopetalum L.	Leonticacea e		Roots	Infusion									
Melilotus indicus (L.) All.	Leguminosa e		Aerial parts, flowers, seeds	Infusion									
Peganum harmala L.	Zygophyllac eae		Leaves	Infusion									
Pluchea dioscoridis (L.) DC.	Compositae		Aerial parts, leaves	Juice									
Ruta graveolens L.	Rutaceae		Leaves	Infusion									
Salvia multicaulis Vahl	Lamiaceae		Leaves	Infusion									
Solenostemma argel (Delile) Hayne	Asclepiadac eae		Leaves	Infusion									
Teucrium leucocladum Boiss.	Lamiaceae		Leaves	Infusion									
Teucrium polium L.	Lamiaceae		Whole plant	Decoction									

Species	Family	Coun-tries	Part of specie	Traditional preparation way	Adminis-tration	Dose	Informants	Sample size	Type of survey	Quantifi-cation of use	Study period	Results	Reference
Adelobotrys adscendens (Sw.) Triana	Melastomataceae	Belize	-	-	-	-	Traditional healers	-	-	RF (relative frequency): Number of traditional practitioners using species/total number of traditional practitioners	June 2003	RF>0.333 RF>0.333 RF>0.333 RF>0.333 RF>0.333 RF<0.333 RF>0.333 RF<0.333 RF>0.333 RF>0.333 RF>0.333 RF>0.333 RF>0.333 RF>0.333 RF<0.333 RF<0.333 RF<0.333 RF>0.333 RF>0.333 RF<0.333 Relative frequency> 0.033 significates a high traditional medicine use	Awad et al., 2009
Adiantum latifolium Lam.	Adiantaceae												
Adiantum princeps T. Moore	Adiantaceae												
Adiantum tetraphyllum Humb. & Bonpl. ex Willd.	Adiantaceae												
Adiantum wilsonii Hook.	Adiantaceae												
Aristolochia grandiflora Sw.	Aristolochiaceae												
Gonzalagunia rosea Standl.	Rubiaceae												
Justicia albobracteata Leonard	Acanthaceae												
Justicia aurea Schltdl.	Acanthaceae												
Justicia pectoralis Jacq.	Acanthaceae												
Lygodium heterodoxum Kunze	Schizaeaceae												
Lygodium venustum Sw.	Schizaeaceae												
Petiveria alliacea L.	Phytolaccaceae												
Piper amalago L.	Piperaceae												
Piper tuerckheimii C.DC	Piperaceae												
Pityrogramma calomelanos (L.) Link	Adiantaceae												
Porophyllum ruderale (Jacq.) Cass.	Compositae												
Baccharis inamoena Gardner	Compositae												

Psychotria tenuifolia Sw.	Rubiaceae												
Selaginella stellate Spring	Selaginellaceae												
Stachytarpheta frantzii Pol.	Verbenaceae												
Moringa oleifera Lam.	Moringaceae	Nigeria	Leaves and bark	Decoction	PO	-	60% men	745	Face-to-face interviews, semi-structured questionnaires	Fidelity level	March 2011 to January 2013	FL : 70 % Traditional medicine and other uses in Nigeria	Popoola et al., 2013

Species	Family	Coun - tries	Part of specie	Traditional preparation way	Adminis- tration	Doses	Informants	Sample size	Type of survey	Quantifi- cation of use	Study period	Results	Reference
Inula cappa (Buch.-Ham. ex D.Don) DC.	Compo sitae	Nepal	Roots	Juice	PO	-	Men and women, including 2 traditional practitioners and 3 elders	62	Structured questionnair es and discussion with villagers	Frequency of citations	August to Decem ber 2000	Frequency of citations : 9.7 % Traditional medicine use in Nepal	Shrestha et al., 2003
Calotropis procera (Aiton) Dryand.	Asclepi adacea e	Burki na Faso	Roots	Pulverization, maceration, decoction	-	-	Traditional healers (aged 35 to 76)	41	Semi-structured interviews	Number of citations	May to Septem ber 2007 and 2008	Number of citations : 15 for both plants Traditional medicine use in Burkina Faso	Nadembeg a et al., 2011
Combretum micranthum G.Don	Combr etacea e		Leaves, branches	Maceration									
Parkinsonia aculeata L.	Cesalpi naceae	Brazil	Bark, roots, flowers, sedes, raffia	-	-	-	-	-	-	RI (relative importance), NCS (number of body system treated), NP (number of pharmacolog ical properties)		RI : 1.2 RI > 1: widely used plant and she has many other pharmacological characteristics Traditional medicine use in Brazil	De Albuquerq ue et al., 2007
Asparagus racemosus Willd.	Aspara gaceae	India	Tuberous roots, whole plant	Decoction	-	2 full s 2/day during 1 month / 10ml 2/day during 1 month	Men and women: village chiefs, traditional practitioners, religious and farmers (aged 45 to 70)	84	Semi-structured questionnair es	RFC (relative frequency of citation), RI (relative importance), CI (cultural index)	Januar y 2009 to June 2011	*Asparagus racemosus* RFC: 0.36 / RI: 0.34/ CI: 0.12 *Citrus maxima* RFC: 0.14 / RI: 0.32 RI<0.5: low used plant in India	Sharma et al., 2012
Citrus maxima (Burm.) Merr.	Rutace ae		Leaves, fruit	Extraction									
Mikania glomerata Spreng.	Compo sitae	Brazil	-	-	-	-	-	-	-	RI (relative importance)	-	RI: 0.84 Moderated traditional medicine use in Brazil	Medeiros et al., 2013

Species	Family	Coun-tries	Part of specie	Traditional preparation way	Adminis-tration	Doses	Informants	Sample size	Type of survey	Quantifi-cation of use	Study period	Results	Reference
Adiantum latifolium Lam.	Adiantaceae	Belize	Leaves (for all plants)	Maceration	PO and topic (for all plants)	-	Traditional healers (aged 53 to 79)	6		FIC (Consensus factor) and percentage of traditional healers who used the specie	June 2003	FIC: 0.429 Percentage of traditional healers use for the specie P: 100 % P: 83,33 % P: 83,33 % P: 83,33 % P: 66,67 % P: 100 % P: 83,33 % P: 83,33 % P: 66,67 % Specific traditional medicine use for epilepsy in Belize	Herbario nacional, 2005
Adiantum princeps T. Moore	Adiantaceae			Maceration									
Adiantum tetraphyllum Humb. & Bonpl. ex Willd.	Adiantaceae			Maceration									
Adiantum wilsonii Hook.	Adiantaceae			Maceration									
Aristolocha grandiflora Sw.	Aristolochiaceae			Maceration and decoction									
Justicia aurea Schltdl.	Acanthaceae			Maceration									
Lygodium heterodoxum Kunze	Schizaeaceae			Maceration									
Lygodium venustum Sw.	Schizaeaceae			Maceration									
Selaginella stellata Spring	Selaginellaceae			Maceration and decoction									
Allium cepa L.	Amaryllidaceae	India	Bulb	Paste (for all the plants)	Inhalation / inhalation / inhalation	-	Informants in 2 different areas	110	Semi-structured questionnaires	Percentage of citations for the disease (%Cm) and Index of specialization (ISU)	-	%Cm: 71% and ISU: 2,27 = High index of specialization %Cm: 100% and ISU: 1,98 = High index of specialization %Cm: 52% and ISU: 1,04 = Moderate index of specialization %Cm: 100% et ISU: 0,76 = Low index of specialization	Ningthoujam et al., 2013
Allium sativum L.	Amaryllidaceae		Bulb										
Cinnamomum camphora (L.) J.Presl	Lauraceae		Leaves										
Ferula assa-foetida L.	Apiaceae		Oleoresin										

Nicotiana glauca Graham	Solanaceae	South Africa	Leaves	Crude	Topic / PO / PO	-	Elders who know the plants	24		Cultural importance index (CII), Relative Frequency of Citation (RFC), Species Popularity Index (SPI)	-	CII: 0.83; RFC: 0.61; SPI: 0,73 CII: 0.57; RFC 0.30; SPI: 0,38 CII: 0,22; RFC: 0,09; SPI: 0,19 Traditional medicine use in South Africa	MacKinney et al., 2015
Pteronia camphorata (L.) L.	Compositae		Leaves	Dry powder									
Limeum africanum L.	Molluginaceae		-	Decoction									

Species	Family	Countries	Part of specie	Traditional preparation way	Administration	Doses	Informants	Sample size	Type of survey	Quantification of use	Study period	Results	Reference
Ajuga integrifolia Buch.-Ham.	Lamiaceae	Ethiopia	Leaves	Pulverization and mix with nut oil	PO	-	Traditional practitioners (men and women) and community members	195	Field observations, semi-structured interviews	Fidelity level (FL)		High fidelity level Traditional medicine use in Ethiopia	Woldeamanuel et al., 2014

CI: cultural index, CII: cultural importance index, FIC: consensus factor, FL: fidelity level, Ip: performance index, I/P: number of interview/ number of inhabitants, ISU: index of specialization, NCS: number of body system treated, NP: number of pharmacological properties, %Cm: percentage of citations for the disease, PO: *per os*, s: spoon, RF: relative frequency, RFC: relative frequency of citation, RI: relative importance, SPI: species popularity index, UV: use value

Table 6. Repartition of species parts used, preparation, administration by continents

	Africa		Latin America		Asia		
	Number	Frequency (%)	Number	Frequency (%)	Number	Frequency (%)	p
Part of vegetal species							
Barks	22	11.6	3	7.3	12	5.9	<0.001
Leaves	74	39.2	21	51.2	46	22.7	
Roots	66	34.9	3	7.3	49	24.1	
Others	27	14.3	14	34.1	96	47.3	
Total	189	100.0	41	100.0	203	100.0	
Preparation mode							
Decoction	76	54.7	13	38.2	30	20.5	<0.001
Infusion	20	14.4	10	29.4	9	6.2	
Powder	18	12.9	0	0.0	33	22.6	
Paste	10	7.2	0	0.0	24	16.4	
Others	15	10.8	11	32.4	50	34.3	
Total	139	100.0	34	100.0	146	100.0	
Administration route							
Per os	92	80.0	25	78.1	162	91.0	0.0128
Others	23	20.0	7	21.9	16	9.0	
Total	115	100.0	32	100.0	178	100.0	
Mechanism of action							
Yes	52	70.3	11	44.0	24	48.0	0.0132
Total	74	100.0	25	100.0	50	100.0	

Table 7. Species most mentioned in *in vitro* or *in vivo* models

Species	Family	Coun-tries	Part of specie	Prepa-ration way	Type of models	Name of models	Extracts	Adminis-tration	Doses (mg/kg)	Gold stan-dard	Observed criteria	Toxici ty	Results	Reference
Gastrodia elata Blume	Orchidaceae	China	Roots	Infusion	*In vivo* & *vitro*	PTZ & GABA transaminase assay	Methanolic	PO	-	VPA	Intensity and duration of seizures, convulsions latency, amount of GABA/ inhibition of GABA transaminase	-	PTZ : ↓ time recovery and severity crisis. No significant action on latency + duration. In vitro: ↑ GABA / inhibition GABA transaminase / Inhibitor effect of lipid peroxidation	Ha et al., 2010
Arctopus echinatus L.	Apiaceae	South Africa, Zimbabwe	Roots	Decoction, juice	*In vitro*	3H-Ro binding test	Ethanolic	-	-	Diazepam	Link to the GABA-A receptor	-	Significant liaison	Stafford et al., 2015
Cotyledon orbiculata L.	Crassulaceae		Leaves	Decoction, juice										
Artemisia afra Jacq. ex Willd.	Compositae		Leaves	Decoction, juice										
Dioscorea dregeana (Kunth) T.Durand & Schinz	Dioscoreaceae		Leaves	Decoction, juice										
Acacia sieberiana DC.	Leguminosae		Bark	Decoction, juice										
Vitex negundo L.	Verbenaceae	India	Leaves	Maceration	*In vivo*	MES, PTZ	Ethanolic	PO	250, 500 et 1000	Diphenylhydantoin, VPA	Duration extension phase	-	Potentiation : ↑ AE activity of VPA	Tandon et al., 2015
Acorus calamus L.	Araceae	India	-	-	*In vivo*	MES, PTZ	Methanolic, ethanolic, oil	PO	100 et 200	-	Intensity and duration of seizures	Mutagen Hepatocarcinogen	AE activity via GABA and sodium channel inhibition	Rajput et al., 2014
Kalanchoe crenata (Andrews) Haw.	Crassulaceae	Cameroun	Leaves	Maceration	*In vivo*	PTZ, Strychnine, thiosemicarbazide	Methanolic	PO	150, 300, 600	CBZ, VPA	Duration and latency of seizures	-	Significant AE effect on latency of seizures more important than CBZ and VPA	Nguelefack et al., 2006

Species	Family	Coun-tries	Part of specie	Prepa-ration way	Type of models	Name of models	Extracts	Administ ration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference
Tetrapleura tetraptera (Schum. & Thonn.) Taub	Leguminosae	South Africa	Fruit	-	*In vivo*	PTZ, picrotoxine, bicuculline	Aqueous	IP	50, 100, 200, 400, 800 mg/kg	Phenobarbitone, Diazepam	Percentage of protection against seizures and latency of convulsions	-	Dose-dependent effect on protection against seizures and latency of convulsions	Ojewole et al., 2005
Delphinium denudatum Wall. ex Hook.f. & Thomson	Ranunculaceae	Pakistan	Roots	-	*In vivo*	MES, PTZ, bicuculline, picrotoxine, strychnine	Aqueous	IP	100, 400, 600 mg/kg	Phenytoin, VPA	Percentage of protection against seizures, latency of convulsions and mortality	-	Dose dependent effect on all models except for strychnine	Raza et al., 2001
Leonotis leonurus (L.) R.Br	Lamiaceae	South Africa	Leaves	Smoking	*In vivo*	PTZ, picrotoxine, bicuculline, NMDA	Aqueous	IP	100, 200, 400 mg/kg	Diazepam, Phenobarbitone	Percentage of protection against seizures and latency of convulsions	-	Dose dependent effect on all models except for bicuculline	Bienvenu et al., 2002
Benkara malabarica (Lam.) Tirveng.	Rubiaceae	India	Roots	-	*In vivo & In vitro*	Strychnine, isoniazid, NMDA	Methanolic	PO	25 et 50 mg/kg	Phenytoin, diazepam	Percentage of protection against seizures and GABA transaminase inhibition	LD 50 > 500 mg/kg	Dose dependent effect on NMDA and isoniazid	Mishra et al., 2010
Carissa spinarum L.	Apocynaceae	Nigeria	Bark of roots	-	*In vivo & In vitro*	PTZ, MES, naloxone and flumazenil	Ethanolic	IP	5, 10, 20 mg/kg	Diazepam, phenytoin	Percentage of protection against seizures and competitive studies with naloxone and flumazenil	LD 50 IP: 282.8 mg/kg and LD 50 PO > 5 g/kg	Protective effect and competitive interaction	Ya'u et al., 2008
Delphinium nordhagenii Wendelbo	Ranunculaceae	Pakistan	Aerial parts	-	*In vivo*	PTZ, picrotoxine, MES	Acetonic	IP	60, 65, 70, 100 mg/kg	Diazepam, phenytoin	Percentage of protection against seizures and latency of convulsions	-	Effect on protection against seizures and latency of convulsions	Raza et al., 2010
Harpagophytum zeyheri (Engl.) Ihlenf. & H.E.K.Hartmann	Pedaliaceae	South Africa	Roots	-	*In vivo*	PTZ, picrotoxine, bicuculline	Aqueous	IP	de 50 à 800 mg/kg	Phenobarbitone, diazepam	Percentage of protection against seizures, latency and duration of convulsions	-	Effect on protection against seizures, latency and duration of convulsions	Mahomed et al., 2006

Species	Family	Coun-tries	Part of specie	Prepa-ration way	Type of models	Name of models	Ex-tracts	Adminis-tration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference

Erythrina verna Vell.	Leguminosae	Brazil	Bark of trunk	-	*In vivo*	PTZ, strychnine	-	IP, PO	200, 400 mg/kg	-	Percentage of protection against seizures, latency of convulsions and mortality	-	No effect on protection against seizures / Effect on latency and mortality	Vasconcelos et al., 2007
Erythrina velutina Willd.	Leguminosae		Bark of trunk						200, 400 mg/kg					
Justicia extensa T.Anderson	Acanthaceae	Nigeria	Leaves	-	*In vivo*	Strychnine, picrotoxine	Methanolic	PO	50, 100, 200 mg/kg	Diazepam, phenobarbitone	Percentage of protection against seizures, latency and duration of convulsions	No toxicity at doses used in the study	No effect on protection against seizures / Effect on latency and duration	Sowemimo et al., 2011
Valeriana officinalis L.	Valerianaceae	Iran	Roots	-	*In vivo*	MTLE	Aqueous and ether petroleum	IP	50 à 800 mg/kg	-	Latency and duration of seizures, post-seizures discharges	-	Aqueous extract: anti-convulsant effect (effect on latency, duration and post-discharges seizures). Mechanism by adenosine A1 receptor – for the partial seizures. Ether extract: pro-convulsant	Rezvani et al., 2010
Marsilea quadrifolia L.	Marsileaceae	India	Whole plant	Maceration	*In vivo*	PTZ	Aqueous and ethanolic	PO	100, 200, 400 mg/kg	Diazepam	Electroencephalogram profile, latency, duration and intensity of seizures	Safety dose: 1000 mg/kg	Dose-dependent effect on severity score, latency, duration of seizures and epileptiform activity. Ethanolic extract more active than aqueous extract	Sahu et al., 2012
Rhus chirindensis Baker f.	Anacardiaceae	South Africa	Barks and stem	Decoction and infusion	*In vivo*	PTZ, bicucculline, picrotoxine	Aqueous	IP	50, 100, 200, 400, 800 mg/kg	Diazepam, phenobarbitone	Percentage of protection against seizures and latency of convulsions	LD 50: 1574 mg/kg	Dose dependent effect on protection and latency. Sedative and hypnotic effect	Ojewole et al., 2008
Piper guineense Schumach. & Thonn.	Piperaceae	Nigeria	-	Powder	*In vivo*	PTZ, MES	Aqueous and ethanolic	IP	-	Phenobarbitone	Percentage of protection against seizures	Rotarod test (neurotoxicity): no difference with controls	Protective effect on MES	Abila et al., 1993

Species	Family	Coun-tries	Part of specie	Prepa-ration way	Type of models	Name of models	Extracts	Adminis-tration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference
Magnolia grandiflora L.	Magnoliaceae	Mexico	Seeds	-	*In vivo*	MES	Ethyl ether, hydro alcoholic	PO	10 à 1000 mg/kg	-	Percentage of protection against seizures, duration and latency of convulsions	Acute toxicity: no neuro-deficiency	Effect on protection, latency and duration on recuperation of orthostatism and extension reflexes	Bastidas Ramirez et al., 1998
Cyperus articulatus L.	Cyperaceae	Cameroun	Rhizomes	Decoction	*In vivo*	PTZ, INH, pilocarpine, STN, isoniazid, bicucculline	Methanolic	IP	50 à 2000 mg/kg	Clonazepam, diazepam, carbamazepine	Protection against seizures	At doses of 1000 and 2000 mg/kg: ataxia 1h after admnimistration	Dose dependent effect on PTZ and INH	Bum et al., 2001
Securidaca longepedunculata Fresen.	Polygalaceae	Nigeria	Roots	-	*In vivo*	STN, picrotoxine	Aqueous	PO	100, 200, 400 mg/kg	Phenobarbitone	Latency of seizures and mortality	LD 50 PO: 1,74 g/kg et LD 50 IP: 19,95 mg/kg	Dose dependent effect more important than phenobarbitone on the latency of seizures for the higher dose. Effect on mortality	Adeyemi et al., 2010
Sarcocephalus latifolius (Sm.) E.A.Bruce	Rubiaceae	Cameroun	Bark, leaves, roots, fruit, stem	Decoction	*In vivo*	PTZ, MES, STN	Aqueous	IP	16, 40, 80, 160 mg/kg	Diazepam, clonazepam	Percentage of protection against seizures	-	Dose dependent protection	Ngo Bum et al., 2009

Species	Family	Coun-tries	Part of specie	Prepa-ration way	Type of models	Name of models	Extracts	Adminis-tration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference
Albizia lebbeck (L.) Benth.	Mimosaceae	India	Leaves and bark	Decoction	*In vivo & in vitro*	MES, electrical kindling, PTZ, lithium, pilocarpine, STN	Ethanolic / ether petroleum/ethanolic	IP	20 à 200 mg/kg	Diazepam	Estimated GABA and serotonin rates, percentage of protection against seizures, duration and latency of convulsions	LD 50: 150 mg/kg / LD 50: 500 mg/kg / LD 50 > 1000 mg/kg	Effect on percentage of protection against seizures, duration and latency of convulsions on all models except for strychnine. Rate increase of serotonin and GABA	Kasture et al., 2000
Butea monosperma (Lam.) Taub.	Leguminosae		Flowers and roots	Maceration					20 à 200 mg/kg					
Hibiscus mutabilis L.	Malvaceae		Flowers	Decoction					20 à 200 mg/kg					
Gastrodia elata Blume	Orchidaceae	China	-	-	*In vivo & in vitro*	Kainic acid	Alcoholic	PO	250, 500, 1000 mg/kg	Carbamazepine	Estimated peroxided lipid level, percentage of protection against seizures, convulsions latency, EEG, EMG	-	Increase of peroxided lipids (contribute to oxidative damage). Effect on protection against seizures and latency of seizures	Hsieh et al., 1999
Uncaria Rhynchophylla (Miq.) Miq. ex Havil.	Rubiaceae								250, 500, 1000 mg/kg					
Mondia whitei (Hook.f.) Skeels	Apocynaceae	Nigeria	Leaves, roots	-	*In vivo*	Pilocarpine	Methanolic	-	25, 50, 100 mg/kg	Diazepam	Percentage of protection against seizures, mortality, duration and latency of convulsions	-	No protection against seizures. Effect on latency, duration of seizures and mortality	Fred-Jaiyesimi et al., 2013

Species	Family	Coun - tries	Part of specie	Prepa-ration way	Type of models	Name of models	Extracts	Adminis-tration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference
Lobelia nicotianaefolia Roth ex Schult.	Campanulaceae	India	Flowers, leaves, roots	-	*In vivo & in vitro*	PTZ, STN, GABA rate	-	IP	5, 10, 20, 30 mg/kg	Diazepam	Percentage of protection against seizures, duration and latency of convulsions	LD 50: 40 mg/kg	Effect on latency and duration of seizures higher with PTZ model. GABA rates decreased at 30 mg/kg and increased at other doses	Tamboli et al., 2012
Viscum capense L. f.	Loranthaceae	South Africa	Stems	-	*In vivo*	PTZ, BIC	Methanolic	IP	50, 100	Phenobarbitone, diazepam	Percentage of protection against seizures and latency of convulsions	-	Effect on latency and protection against seizures	Amabeoku et al., 1998
Stylosanthes erecta P.Beauv.	Leguminosae	Mali	Leaves, aerial parts	-	*In vitro*	GABA A binding study	Ethanolic / dichloromethane	IP	0,1, 1 10 mg/kg	-	Percentage of binding of flumazenil to GABA A receptor	-	Dose dependent binding to receptor GABA A	Bah et al., 2007
Trichilia emetic Vahl	Meliaceae		Roots, bark, leaves						0,1, 1 10 mg/kg					
Viola betonicifolia Sm.	Violaceae	Pakistan	Whole plant	-	*In vivo*	PTZ	Hexane	IP	300, 400, 500 mg/kg	Diazepam	Percentage of protection against seizures and latency of convulsions	-	Dose dependent protection against seizures and latency on PTZ model.	Muhammad et al., 2013
Leonotis leonurus (L.) R.Br.	Lamiaceae	South Africa	-	-	*In vivo*	PTZ	Aqueous	IP	200, 400 mg/kg	Diazepam, phenobarbitone	Percentage of protection against seizures and latency of convulsions	-	Effect on latency and protection against seizures	Fennel et al., 2004
Waltheria indica L.	Malvaceae	Guinea	Roots, stem	-	*In vivo*	PTZ, STN	Aqueous	IP	100, 200 mg/kg	Chlorpromazine	Percentage of protection against seizures and duration of convulsions	-	Effect on duration and protection against seizures	Zongo et al., 2013

Species	Family	Coun - tries	Part of specie	Prepa-ration way	Type of models	Name of models	Extracts	Adminis-tration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference
Bacopa monnieri (L.) Wettst.	Plantaginaceae	India	Whole plant	Juice	*In vivo*	PTZ	-	PO	0,5 ml/rat during 3 months (all the plants)	Diazepam	EEG profile and percentage of protection against seizures	-	Protection against seizures equally effective as diazepam. Restored EEG profile	Shanmugasundaram et al., 1991
Cyperus rotundus L.	Cyperaceae		Bulbous roots	Decoction										
Saussurea costus (Falc.) Lipsch.	Compositae		Roots	Decoction										
Calotropis gigantea (L.) Dryand.	Apocynaceae	India	Roots, flowers, leaves, bark of the stem	Infusion	*In vivo*	MES, PTZ	Aqueous, petroleum ether, methanolic	PO	180, 200 mg/kg	Phenytoin	Percentage of protection against seizures	-	Effect on protection against seizures	Karkiet al., 2010
Calotropis gigantea (L.) Dryand.	Apocynaceae	India	Roots	Infusion	*In vivo*	PTZ	Alcoholic	PO	250, 500 mg/kg	Diazepam	Seizure latency, frequency and extension of posterior limbs	-	Effect on seizure latency, frequency of seizures and reduction of extension of posterior limbs	Argal et al., 2006
Petiveria alliacea L.	Phytolaccaceae	Brazil	Roots	-	*In vivo*	PTZ	Hydro-alcoholic	PO, IP	100 et 200 mg/kg	Diazepam	Percentage of protection against seizures, latency and mortality	-	Protective effect against seizures, effect on seizure latency and mortality more important by IP than PO	Gomes et al., 2008
Mentha aquatica L.	Lamiaceae	South Africa	Aerial parts	-	*In vitro*	GABA binding	Ethanolic and essential oil	-	-	-	Percentage of binding to GABA A receptor	-	Low binding to receptor GABA A	Jäger et al., 2007
Bridelia micrantha (Hochst.) Baill.	Euphorbiaceae	Cameroun	Bark	Decoction	*In vivo*	PTZ, MES, STN, picrotoxine, isoniazid	Aqueous	PO	30 à 305 mg/kg	Clonazepam, diazepam	Percentage of protection against seizures and latency of convulsions	-	Protective effect against seizures on picrotoxine, PTZ, MES and strychnine models and effect on latency of seizures on isoniazid model. Synergic effect with diazepam and clonazepam	Ngo Bum et al., 2012
Croton macrostachyus Hochst. ex Delile	Euphorbiaceae		Bark	Decoction					15 à 135 mg/kg					

Species	Family	Coun-tries	Part of specie	Prepa-ration way	Type of models	Name of models	Extracts	Administration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference
Pericopsis laxiflora (Baker) Meeuwen	Leguminosae	Nigeria	Roots	Decoction	*In vivo*	Picrotoxine, MES	-	IP	50, 100, 150, 200, 250 et 300 mg/kg	-	Percentage of protection against seizures, duration and latency of convulsions	-	Dose dependent effect on latency, duration and protection against seizures	Haruna et al., 2000
Desmodium adscendens (Sw.) DC.	Leguminosae	Gabon	Leaves	Decoction	*In vivo*	PTZ, MES, kainic acid	Methanolic	IP	5, 50, 100, 300, 1000 mg/kg	-	Percentage of protection against seizures, latency of convulsions and mortality	Acute toxicity at 1000 mg/kg: abdominal contractions, decreased motor activity and exploratory behavior	Effect on latency, protection and mortality for tonic (not clonic) seizures on PTZ and kainic acid models but not on MES model.	N'gouemo et al., 1996
Croton penduliflorus Hutch.	Euphorbiaceae	Nigeria	Seeds	-	*In vivo*	PTZ, STN	Oil	IP	6 mg/kg	-	Percentage of protection against seizures and latency of convulsions	-	Absence of protective effect on both models. Effect on latency of seizures on STN model	Asuzu et al., 1989

Species	Family	Coun-tries	Part of specie	Prepa-ration way	Type of models	Name of models	Extract	Admini s-tration	Doses (mg/kg)	Gold standard	Observed criteria	Toxi-city	Results	Reference
Terminalia chebula Retz.	Combretaceae	Iran	Fruit	-	*In vivo & in vitro*	In vivo: PTZ, MES, picrotoxine, pilocarpine, STN, 4-amino pyridine	Hydro alcoholic (all the plants)	PO, IP	200, 500	VPA, diazepam, phenytoin, MES, phenobarbital	Percentage of protection against seizures, duration, amplitude, latency, intensity of convulsions, mortality, convulsions threshold	-	*Terminalia chebula* has an effect on mortality, duration and latency. *Pimpinella anisum* is protective against tonic extension, mortality, increase the threshold and latency of convulsions and decrease amplitude of the discharges *Anacyclus pyrethrum* has a dose dependent protective effect, increase the latency and threshold and decrease the duration of extensions. *Laurus nobilis* is protective against tonic convulsions *Origanum majorana* has an effect on duration and latency *Nigella sativa* has a protective effect and an effect on duration, latency on PTZ and Picrotoxine models. On MES models, there is no effect on latency and duration *Piper longum* has a protective effect, decrease the mortality and increase the latency on PTZ and pilocarpine models. Not on STN and 4-aminopyridine models. *Ferula gummosa* has a protective dose-dependent effect *Ferula assa-foetida* and *Brassica nigra* decreases the intensity and duration *Caesalpinia bonduc* has a protective effect on seizures *Lavandula stoechas* increases the latency, decrease the mortality and severity of seizures *Ruta graveolens* increases latency of tonic and myoclonic seizures	Abdollahi et al., 2013
Pimpinella anisum L.	Compositae		Seeds						200					
Anacyclus pyrethrum (L.) Lag.	Apiceae		Roots						200, 400, 600					
Laurus nobilis L.	Lauraceae		Seeds						-					
Origanum majorana L.	Lamiaceae		Aerial parts						250, 500					
Nigella sativa L.	Renonculaceae		Seeds						250 and 500					
Piper longum L.	Piperaceae		Fruit						250 and 500					
Ferula gummosa Boiss.	Apiaceae		Resin						40 et 80					
Ferula assa-foetida L.	Apiaceae		Resin						2,5, 5, 10, 20, 250, 500 -					
Brassica nigra (L.) K.Koch	Brassicaceae		Fruit						-300, 500, 750					
Caesalpinia bonduc (L.) Roxb.	Cesalpinaceae		Fruit						600, 800					
Lavandula stoechas L.	Lamiaceae		Aerial parts						600					
Ruta graveolens L.	Rutaceae		Aerial parts						100, 300, 500, 800, 1000					

Species	Family	Coun - tries	Part of specie	Prepa- ration way	Type of models	Name of models	Extracts	Adminis- tration	Doses (mg/kg)	Gold standard	Observed criteria	Toxicity	Results	Referenc e
Eryngium foetidum L.	Apiaceae	Carib bean	Leaves, aerial parts	Infusion	*In vivo*	Picrotoxi ne	Aqueous	IP	-	Phenobarbito ne	% protection against seizures	-	AE activity	Paul et al., 2011
Acorus calamus L.	Araceae	India	Roots	Paste	*In vivo*	PTZ, STN, MES	Ethanolic, methanolic	IP, PO	100, 250, 500, 1000	-	% protection against seizures	-	AE activity	Sharma et al., 2013
Allium sativum L.	Amaryllidacea e		Bulb	Decocti on		PTZ	Alcoholic		-					
Asparagus racemosus Willd.	Asparagaceae		Roots	Powder		MES, PTZ	Methanolic, aqueous		200					
Bacopa monnieri (L.) Wettst.	Plantaginacea e		Leaves	Paste, juice, decocti on		MES, PTZ	Ethanolic, aqueous		50, 55, 300					
Boerhavia diffusa L.	Nyctaginaceae		Roots	Powder		PTZ, MES, pilocarpin e, STN	Methanolic		1000, 1500, 2000					
Calotropis gigantea (L.) Dryand.	Apocynaceae		Leaves	Decocti on		PTZ	Methanolic		100, 200					
Datura stramonium L.	Solanaceae		-	Decocti on		MES, PTZ	-		180, 250, 500					
Oxalis corniculata L.	Oxalidaceae		Roots	Decocti on		Pilocarpi ne, Li	Methanolic		-					
Punica granatum L.	Punicaceae		Bark	Decocti on		MES, PTZ, STN	Hydro alcoholic		200, 400					
Rauvolfia serpentina (L.) Benth. ex Kurz	Apocynaceae		-	Infusion		STN, camphor, PTZ	Aqueous		100, 200, 400, 600					
Ricinus communis L.	Euphorbiacea e		Roots	Powder		PTZ, MES	Ethanolic		-					
Vitex negundo L.	Verbenaceae		Seeds, leaves	-		PTZ, MES, STN	Alcoholic petroleum ether		60					

Species	Family	Coun-tries	Part of specie	Prepa-ration way	Type of models	Name of models	Extracts	Adminis-tration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference
Adelobotrys adscendens (Sw.) Triana	Melastomataceae	Belize	-	-	*In vitro*	GABA transaminase assay and GABA A receptor binding	Ethanolic	-	-	Vigabatrin	% inhibition GABA transaminase + % receptor binding GABA A	-	*Adelobotrys adscendens:* % inhibition GABA T: 10% and % receptor binding GABA A: 40% *Adiantum latifolium, Adiantum princeps Adiantum tetraphyllum, Adiantum wilsonii:* Low GABA T inhibition and receptor binding GABA A *Gonzalagunia rosea:* % inhibition and binding higher than other Rubiaceae *Justicia aurea, Justicia pectoralis, Lygodium heterodoxum, Lygodium venustum, Petiveria alliacea:* No effect *Piper amalago, Piper tuerckheimii:* GABA T inhibition relationship / relative frequency of seizures is significant (but not GABA A binding) *Psychotria tenuifolia, Selaginella stellata:* No effect	Awad et al., 2009
Adiantum latifolium Lam	Adiantaceae													
Adiantum princeps T. Moore	Adiantaceae													
Adiantum tetraphyllum Humb. & Bonpl. ex Willd.	Adiantaceae													
Adiantum wilsonii Hook.	Adiantaceae													
Gonzalagunia rosea Standl.	Rubiaceae													
Justicia aurea Schltdl.	Acanthaceae													
Justicia pectoralis Jacq.	Acanthaceae													
Lygodium heterodoxum Kunze	Schizaeaceae													
Lygodium venustum Sw.	Schizaeaceae													
Petiveria alliacea L.	Phytolaccaceae													
Piper amalago L.	Piperaceae													
Piper tuerckheimii C.DC.	Piperaceae													
Psychotria tenuifolia Sw.	Rubiaceae													
Selaginella stellata	Selaginellacea													

Spring	e													
Syzygium aromaticum (L.) Merr. & L.M.Perry	Myrtaceae	Iran	-	-	*In vivo*	PTZ, MES	Essential oil	IP	0,025, 0,05, 0.0625 0,075 and 0,1 ml/kg	Ethosuximide, phenytoin	Threshold of seizures, % protection against seizures and mortality	LD 50: 0,64 ml/kg	Increase of the threshold of seizures on both models and protection against seizures and mortality on MES model	Pourgholami et al., 1999

Species	Family	Coun-tries	Part of specie	Prepa-ration way	Type of models	Name of models	Extracts	Adminis-tration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference
Bacchari s serraefoli a DC.	Composita e	Mexico	Leaves	-	*In vivo*	PTZ, STN	Methanol ic	IP	10, 50, 100, 200, 250mg/ kg	-	Percentage of protection against seizures, latency of convulsions and mortality	-	Protective effect against seizures, effect on latency and mortality	Tortoriello et al., 1996
Millettia thonningii (Schum. & Thonn.) Baker	Leguminos ae	Camerou n	Seeds	Decocti on, infusion	*In vivo*	MES, NMDA, PTZ, INH, picrotoxin e, STN	Methanol ic	IP et PO	100, 200, 500, 1000 mg/kg	Diazepam, clonazepa m	Percentage of protection against seizures and latency of convulsions	-	*Millettia thonningii:* Protective effect on MES (increase the duration of inactivation of , PTZ (effect on clonic generalized seizures which involves GABAergic system), NMDA (effect on generalized tonico-clonic and partial seizures) *Ocimum tenuiflorum:* Protective effect on MES, picrotoxine (complex interaction with NMDA receptor), PTZ, STN (glycine receptors involved) *Securidaca longepedunculata:* Protective effect on PTZ, MES, INH, Picrotoxine, STN	Okomolo et al., 2011
Ocimum tenuifloru m L.	Polygalace ae		Bark of roots	Decocti on			Ethanolic							
Securida ca longeped unculata Fresen.	Polygalace ae		Roots	-			Aqueous							

Species	Family	Coun-tries	Part of specie	Prepa-ration way	Type of models	Name of models	Extracts	Adminis-tration	Dose	Gold standard	Observed criteria	Toxicity	Results	Refe-rence
Zapoteca portoricensis (Jacq.) H.M.Hern.	Mimosaceae	Nigeria	Roots	-	*In vivo*	MES, PTZ	Aqueous	IP	-	-	Latency and duration of convulsions	Acute toxicity with signs of CNS depression : ataxia, incoordination, shortness of breath, psychomotor retardation	Effect on latency and duration of convulsions for all plants. *Zapoteca portoricensis* Therapeutic index (Ti) = 2.1 LD 50 : 587,14 mg/kg *Cleome rutidosperma* Ti = 1.7 - LD 50 : 102 mg/kg *Cynodon dactylon* Ti = 1.6 - LD 50 : 708 mg/kg *Holarrhena floribunda* Ti = 2.9 - LD 50 : 200 mg/kg *Newbouldia laevis* Ti = 3.3 - LD 50 : 550 mg/kg *Tetrapleura tetraptera* Ti= 4.0 - LD 50 : 165 mg/kg	Akah et al., 1997
Cleome rutidosperma DC.	Capparidaceae		Roots											
Cynodon dactylon (L.) Pers.	Poaceae		Leaves											
Holarrhena floribunda (G.Don) T.Durand & Schin	Apocynacées		Leaves											
Newbouldia laevis (P.Beauv.) Seem.	Bignoniaceae		Leaves											
Tetrapleura tetraptera (Schum. & Thonn.) Taub.	Leguminosae		Fruit											
Cyperus articulatus L.	Cyperaceae	Cameroun	Rhizome	Decoction	*In vitro*	NMDA and glycine receptor binding study	Aqueous	-	-	-	Frequency, amplitude of spontaneous discharges and binding to glycine and NMDA receptors	-	Dose dependent response: nonspecific binding to glycine receptors and NMDA. Frequency and amplitude reduction of spontaneous epileptiform discharges, inhibition of number and depolarization induced by NMDA	Bum et al., 1996

Species	Family	Coun-tries	Part of specie	Prepa-ration way	Type of models	Name of models	Extracts	Adminis-tration	Doses	Gold standard	Observed criteria	Toxi-city	Results	Reference
Rubus brasiliensis Mart.	Rosaceae	Brazil	Leaves	-	*In vivo*	PTZ	Hexane fraction	PO	50, 100, 150, 300 mg/kg	Diazepam	Percentage of protection against seizures and flumazenil competition test	-	Prevention of convulsions and induction of muscle relaxation. Binding totally reversible by adding flumazenil	Nogueira et al., 2000
Euphorbia tirucalli L.	Euphorbiaceae	Somalia	Aerial parts	-	*In vivo*	PTZ	Ethanolic	IP	250 mg/kg	-	Percentage of protection against seizures	Maximum tolerated dose in mice: 500 mg/kg	Protective effect	Samuelsson et al., 1992
Jatropha curcas L.	Euphorbiaceae		Roots			PTZ et STN								
Cymbopogon citratus (DC.) Stapf	Poaceae	Brazil	Leaves	Infusion	*In vivo*	PTZ, MES	Essential oil	PO	0.5 et 1 g/kg	Chlordiazepoxide, VPA	Percentage of protection against seizures and latency of seizures	Acute toxicity: no severe toxicity below 1 g/kg then CNS depressant effect	Dose dependent protection against seizures on MES model and increase of latency clonic convulsions. Action on the effectiveness of generalized tonic-clonic seizures by blocking the spread of the seizure but no absence and myoclonic seizures	Blanco et al., 2009
Gardenia resinifera Roth	Rubiaceae	India	Resin	Oil	*In vivo*	PTZ, MES	Essential oil	IP	30, 100, 300 mg/kg	Phenobarbitone	Percentage of protection against seizures, duration, latency of seizures, recovery time and mortality	Acute toxicity: LD 50 > 5 ml/kg	Dose-dependent and significant increase of the latency of seizures and percentage of seizures on PTZ model. Increase of the latency and decrease of recovery time on MES model. Protection against mortality. Effect increasing convulsive threshold and by blocking the propagation of seizures by GABAergic system.	Shareef et al., 2013

Species	Family	Coun-tries	Part of specie	Prepa-ration way	Type of models	Name of models	Extracts	Adminis-tration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference
Uncaria rhynchophylla (Miq.) Miq. ex Havil	Rubiaceae	Taiwan	-	-	*In vitro & in vivo*	Kainic acid : epileptiform discharges and protein study	Alcoholic	PO	1 g /kg	-	EEG and EMG detection	-	Decrease of the amplitude of action potential from pyramidal neuron, decrease neuronal death, modifies the expression of glial cells in particular by a mechanism involving glial proliferation	Lin et al., 2011
Qualea grandiflora Mart.	Vochysiaceae	Brazil	Leaves	-	*In vivo*	PTZ	Hydro alcoholic	IP	100, 300, 500 mg/kg	Phenobarbitone	Percentage of protection against seizures, latency, intensity of seizures and mortality	LD 50: 1,321 mg/kg	Protective effect against clonic seizures, mortality and increase of the seizures latency	Gaspi et al., 2006

Species	Family	Coun - tries	Part of specie	Prepa-ration way	Type of models	Name of models	Extract	Adminis-tration	Doses	Gold standard	Observed criteria	Toxi-city	Results	Reference
Alchornea cordifolia (Schumach. & Thonn.) Müll.Arg.	Euphorbiaceae	Mali	Leaves	-	*In vitro & in vivo*	Recording of electrical potentials between cortical part and callosum and benzodiazepine receptor-specific binding test (9 first plants) AND PTZ for 2 last	Ethanolic	PO (PTZ)	200, 800, 1600 mg/kg (PTZ)	-	Electrical potentials and binding to benzodiazepin receptor	-	*Alchornea cordifolia* : binding to benzodiazepin receptor *Balanites aegyptiaca* : Dose dependent inhibition of spontaneous epileptiform discharges but no benzodiazepin receptor binding *Burkea africana* : binding to benzodiazepin receptor *Bridelia ferruginea* : Dose dependent inhibition of spontaneous epileptiform discharges with benzodiazepine receptor binding *Ozoroa insignis* : binding to benzodiazepine receptor *Pseudocedrela kotschyi* : binding to benzodiazepin receptor *Terminalia macroptera* : Dose dependent inhibition of spontaneous epileptiform discharges with benzodiazepine receptor binding *Pteleopsis suberosa* : idem than *Terminalia macroptera* *Guiera senegalensis* : idem than *Terminalia macroptera* *Psorospermum senegalense* : The greatest in vitro activity (dose dependent inhibition of spontaneous epileptiform discharges with benzodiazepine receptor binding) – No activity on seizures induced by PTZ *Flueggea virosa* : idem than *Psorospermum senegalense*	Pedersen et al., 2009
Balanites aegyptiaca (L.) Delile	Zygophyllaceae		Bark											
Burkea africana Hook.	Cesalpinaceae		Leaves											
Bridelia ferruginea Benth.	Euphorbiaceae		Bark											
Ozoroa insignis Delile	Anacardiaceae		Leaves											
Pseudocedrela kotschyi (Schweinf.) Harms	Meliaceae		Roots											
Terminalia macroptera Guill. & Perr.	Combretaceae		Roots											
Pteleopsis suberosa Engl. & Diels	Combretaceae		Leaves											
Guiera senegalensis	Combretaceae		-											

J.F.Gmel														
Psorospermum senegalense Spach	Hypericaceae		Roots											
Fluegga virosa (Roxb. ex Willd.) Royle	Phyllanthaceae		Leaves											

Species	Family	Coun - tries	Part of specie	Prepa- ration way	Type of models	Name of models	Extract	Adminis- tration	Doses	Gold stan- dard	Observed criteria	Toxi- city	Results	Reference
Rhoicissus tridentata (L.f.) Wild & R.B.Drumm	Anacardiaceae	South Africa	Leaves	-	*In vitro & in vivo*	Binding to GABA receptor / Binding to GABA receptor / PTZ and binding to GABA receptor / Binding to GABA receptor / PTZ, picrotoxine, NMDA, bicuculline and binding to GABA receptor / Binding to GABA receptor	Ethanolic	-	0,001, 0,01, 0,1, 1, 10 mg/ml	-	Percentage of binding to receptor GABA A and protection against seizures	-	*Rhoicissus tridentate* : Binding at 96 % *Rhus rehmananniana :* Binding at 96 % *Hoslundia opposite :* Binding at 95 % and 60 % of protection against seizures *Clausena anisate :* Binding at 91 % *Leonotis leonurus :* 110 % of protection against seizures on PTZ, picrotoxine, NMDA and not bicuculline *Leonotis leonurus:* Binding at 107 %	Risa et al., 2004
Rhus rehmananniana Engl.	Anacardiaceae		Leaves				Ethanolic							
Hoslundia opposita Vahl	Lamiaceae		Leaves				Ethanolic							
Clausena anisata (Willd.) Hook.f. ex Benth.	Rutaceae		Roots				Ethanolic							
Leonotis leonurus (L.) R.Br.	Lamiaceae		Roots				Aqueous and ethanolic							
Leonotis leonurus (L.) R.Br.	Lamiaceae		Bulb				Ethanolic							
Dorstenia arifolia Lam.	Moraceae	Brazil	Rhizome	-	*In vivo*	PTZ	Methanolic	IP	10, 30, 50 mg/kg	Phenobarbital	Percentage of protection against seizures, latency, duration and mortality	-	Dose dependent protective effect, reduction of the mortality, increase of the latency but no effect on the duration of seizures	Zapata-Sudo et al., 2010
Spondias mombin L.	Anacardiaceae	Nigeria	Leaves	-	*In vivo*	STN, picrotoxine	Ethanolic, methanolic, aqueous	IP	25, 50, 100 mg/kg	Phenobarbital	Percentage of protection against seizures	LD 50 methanolic: 1,1 g/kg et ethanolic: 480 mg/kg	Protective effect on picrotoxine model for ethanolic extract, no effect on STN model and no effect of the aqueous extract	Ayoka et al., 2006

Species	Family	Coun-tries	Part of specie	Prepa-ration way	Type of models	Name of models	Extracts	Adminis-tration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference
Searsia dentata (Thunb.) F.A.Barkley	Anacardiaceae	South Africa	Leaves	-	*In vitro*	Antagonist effect on NMDA receptors	Ethanolic	-	0,1 mg/ml	-	Binding to NMDA receptors	-	Dose-dependent and specific reduction of the NMDA membrane currents of cerebral granular neurons	Marchetti et al., 2011
Searsia pyroides (Burch.) Moffett	Anacardiaceae													
Gladiolus dalenii Van Geel	Iridaceae	Cameroun	-	Maceration	*In vitro & in vivo*	GABA concentration in the brain, PTZ, MES	Lyophilized and aqueous extract	PO	150, 1000 mg/kg	Clonazepam, diazepam	Concentration measure of intra-cerebral GABA, flumazenil inhibition test, percentage of protection against seizures	High LD 50: 9332 mg/kg. No toxic effect.	Protective effect (100 % against seizures induced by PTZ and 83.3 % with seizures induced by MES). Anti-convulsant effect antagonized by flumazenil. Increase concentration dependent of the GABA level : action on tonic-clonic generalized seizures (via GABA A transmission) and idiopathic generalized seizures (via inactivation of sodium channels)	Ngoupaye et al., 2013
Mitragyna Africana (Willd.) Korth.	Rubiaceae	Nigeria	Bark of stem	-	*In vivo*	STN	Methanolic	IP	400 mg/kg	-	Percentage of protection against seizures and latency	LD 50 not determinable because no mortality	Protection at 40 % against seizures & increase of 77 % of the latency of seizures	Aji et al., 2001

Species	Family	Coun - tries	Part of specie	Prepa- ration way	Type of models	Name of models	Extracts	Adminis- tration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference
Searsia dentate (Thunb.) F.A.Barkley	Anacardiaceae	South Africa	Leaves	-	*In vitro*	Binding to NMDA and AMPA receptors	Ethanolic	-	-	-	Spontaneous epileptiform discharge and binding to NMDA and AMPA receptors	-	Dose dependent inhibition of spontaneous epileptiform discharge. Inhibition of the depolarization induced by NMDA and not AMPA	Pedersen et al., 2008
Searsia pyroides (Burch.) Moffett	Anacardiaceae													
Acanthus montanus (Nees) T.Anderson	Acanthaceae	Cameroun	Leaves	Decoction	*In vivo*	MES, PTZ, NMDA, INH, Pilocarpine, STN	Aqueous	PO & IP	100, to 1000 mg/kg / 12 to 120 mg/kg / 16 to 160 mg/kg 33 to 260 mg/kg 10 to 100 mg/kg 14 to 140 mg/kg	Clonazepam, diazepam	Percentage of protection against seizures and latency	-	*Acanthus montanus:* Protective effect on all models except for NMDA *Alchornea laxiflora:* Protective effect on NMDA (100%) and STN (75%) *Hyptis spicigera:* Protective effect on PTZ (87.5%) and STN (100%) *Microglossa pyrifolia:* High protective effect on all models, more moderated on STN (50%) *Bauhinia reticulate:* Protective effect on NMDA (100%), PTZ (32.5%), STN (75%) *Voacanga africana:* Protective effect on all models except for PIC	Bum et al., 2009
Alchornea laxiflora (Benth.) Pax & K.Hoffm.	Euphorbiaceae													
Hyptis spicigera Lam.	Lamiaceae													
Microglossa pyrifolia (Lam.) Kuntze	Compositae													
Bauhinia reticulata DC.	Cesalpinaceae													
Voacanga africana Stapf ex Scott-Elliot	Apocynaceae													
Lannea barteri (Oliv.) Engl.	Anacardiaceae	Nigeria	Stem	-	*In vivo*	PTZ, STN, Pilocarpine, MES	Ethanolic	IP	80 and 160 mg/kg	VPA	Percentage of protection against seizures and latency	LD 50: 565,7 mg/kg	Significant protective effect on all models except for MES	Garba et al., 2015

Species	Family	Coun-tries	Part of specie	Prepa-ration way	Type of models	Name of models	Extracts	Administ ration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference
Carissa spinarum L.	Apocynaceae	Nigeria	Roots	-	*In vivo*	PTZ, Pilocarpine, NMDA, aminophylline, INH, STN, HEK embryonal cells	Ethanolic	IP	150, 300, 600 mg/kg	VPA	Observation of clonic spasms, latency prolongation and onset of seizures, abolition of clonic extension, 360° circles of the animal, myoclonic seizures, mortality	LD 50: 2222.61 mg/kg	Significant protective effect on PTZ and aminophylline models	Ya'u et al.; 2015
Solanum torvum Sw.	Solanaceae	Philippines	Aerial parts	Aqueous decoction	*In vivo*	PTZ, Pilocarpine, NMDA, aminophylline, INH, STN, HEK cells	Aqueous and methanolic	PO & IP	280 µmol/L	-	Reduction of the movements	-	Activity on PTZ model	Challal et al., 2014

Species	Family	Coun-tries	Part of specie	Prepa-ration way	Type of models	Name of models	Ext-racts	Admini-stration	Dose s	Gold standard	Observed criteria	Toxicity	Results	Reference
Ficus platyphylla Delile	Moraceae	Nigeria	Bark	-	*In vivo*	PTZ, pilocarpine, INH, STN, aminophylline, MES	Methanolic	IP	200, 400 mg/kg	Phenobarbitone	Locomotor activity, latency and duration of sleep, motor coordination, protection against tonic-clonic, tonic and myoclonic seizures, mortality	LD50 > 5000 mg/kg	Reduction of the locomotor activity, no significant effect on latency and sleep duration, no effect on motor coordination. PTZ: Protection dose dep / MES: No protection / PCT: protection against myoclonic and tonic attacks and mortality / INH: no protection but increases the latency of seizures / STN: seizures and mortality dependent dose protection / aminophylline: protection against mortality but no protection against seizures	Chindo et al., 2014
Telfairia occidentalis Hook.f.	Cucurbitaceae	Nigeria	Leaves	-	*In vivo*	INH, STN	Hydro-ethanolic	PO	25, 50, 100, 200, 400, 800 mg/kg	Diazepam	Mortality, duration and latency of seizures	LD 50 IP: 3162.28 mg/kg and decreased locomotion, loss of pupillary reflexes and breathing frequency. LD 50 PO: 10g/kg. No mortality or signs of toxicity.	Reduction of the duration and increase of the latency of seizures on STN model. No effect on latency and duration but decrease the mortality on INH model	Akindele et al., 2013

AE: anti-epileptic, AMPA: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, GABA: gamma-aminobutyric acid, HEK: human embryonic kidney, INH: isoniazid, IP: intra peritoneal, MES: maximal electroshock seizure, MTLE: mesial temporal lobe epilepsy, NMDA: N-Methyl-D-Aspartate, PO: *per os*, PTZ: pentenyltetrazole, STN: strychnine, VPA: valproic acid

Table 8. Prevalence of epilepsy related to number of plant use reports by country

Country	Number of use reports	Prevalence	Reference
Latin America			
Belize	30	-	-
Bolivia	3	12.6/1000	Bruno et al., 2013
Brazil	9	13.0/1000	Bruno et al., 2013
Caribbean	1	7.5/1000	Bruno et al., 2013
Mexico	2	19.5/1000	Bruno et al., 2013
Panama	2	22.5/1000	Bruno et al., 2013
Peru	19	20.9/1000	Bruno et al., 2013
Asia			
Bangladesh	1	-	-
China	4	4.4/1000	Mac et al., 2007
India	196	4.7/1000	Mac et al., 2007
Iran	15	-	-
Nepal	1	7.3/1000	Mac et al., 2007
Pakistan	3	10.0/1000	Mac et al., 2007
Philippines	1	-	-
Taiwan	1	2.8/1000	Mac et al., 2007
Africa			
Burkina Faso	2	10.6/1000	Ba Diop et al., 2014
Cameroon	16	35.4/1000	Ba Diop et al., 2014
Egypt	17	-	-
Ethiopia	4	29.5/1000	Ba Diop et al., 2014
Gabon	1	-	-
Guinea	1	-	-
Kenya	4	3.8/1000	Ba Diop et al., 2014
Mali	13	13.3/1000	Ba Diop et al., 2014
Nigeria	22	6.2/1000	Ba Diop et al., 2014
Sahara	4	-	-
Somalia	7	-	-
South Africa	28	3.4/1000	Ba Diop et al., 2014
Tanzania	81	7.2/1000	Ba Diop et al., 2014
Uganda	8	5.0/1000	Ba Diop et al., 2014
Zimbabwe	1	-	-