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

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► To cite this version:

Emilie Auditeau, François Chassagne, Geneviève Bourdy, Mayoura Bounlu, Jérémy Jost, et al.. Herbal medicine for epilepsy seizures in Asia, Africa and Latin America: A systematic review. *Journal of Ethnopharmacology*, 2019, 234, pp.119-153. 10.1016/j.jep.2018.12.049 . hal-02017365

HAL Id: hal-02017365

<https://unilim.hal.science/hal-02017365v1>

Submitted on 21 Oct 2021

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31 **ABSTRACT**

32

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

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

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

49 *Results:* The search yielded 1886 articles, from 30 countries. Hundred and six articles published
50 between 1982 and 2017 were included, corresponding to a total of 497 use reports for 351 plant
51 species belonging to 106 families. Three hundred and seventy seven use reports corresponding to
52 264 species in ethnopharmacological surveys and 120 evaluation reports corresponding to 107
53 species were noted. Twenty-nine reports, for 29 species, combined both ethnopharmacological and
54 pharmacological evaluation. Fifty eight studies originated from Africa, 35 studies from Asia and 18
55 from Latin America. Highest use report was noted for rhizomes of *Acorus calamus* L. (12 use report in
56 1 country) and leaves of *Bacopa monnieri* (L.) Wettst. (8 use report in 2 countries). Therefore these
57 species display the highest use convergence. Regarding pharmacological evaluation most studied
58 species were: *Leonotis leonurus* (L.) R.Br. (4 evaluation reports in 1 country), *Uncaria rhynchophylla*
59 (Miq.) Miq. ex Havil. (3 evaluation reports in 2 countries) and *Calotropis gigantea* (L.) Dryand. (3
60 evaluation reports in 1 country). *In vivo* models of chronic epilepsy were more relevant than *in vitro*
61 models or chemical models inducing acute seizures for pharmacological assessment.

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

65

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

68

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88 1. Background

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

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

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

138 2. Methodology

139 2.1 Search strategy

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

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

156 2.2 Eligibility criteria

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

160 2.2.1. Inclusion criteria

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

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

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

166 (3) Types of studies criteria:

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

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

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

180 (5) Nomenclature: We checked all plants in The Plant List and we added standardized names from
181 the list into the main text, tables and figures, following the current recommendations (Rivera et al.,
182 2014),

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

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

187 2.2.2. Exclusion criteria

188 Studies meeting the following criteria were excluded:

189 (1) To include participants with others neurological diseases,

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

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

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

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

197 2.3 Data collection

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

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

204 The following data were collected:

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

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

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

211

212 For each type of studies, we collected specific data:

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

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

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

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

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

225 *2.4 Data analysis*

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

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

231 In order to identify and select species with high use convergence, their use report was evaluated.

232 For ethnopharmacological surveys, it was defined by the expression:

233
$$\textit{One use report} = \textit{One species} + \textit{One part of plant} + \textit{One geographical location}$$

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

236

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

238
$$\textit{One evaluation report} = \textit{One species} + \textit{One part of plant} + \textit{One preclinical test}$$

239

240 The statistical analyses were performed using Stata 12® software (Stata Corporation, College Station,
241 TX, USA). We performed Chi² test for dichotomous variables. Yates correction were used when
242 expected numbers were ranged from 2.5 to 5 or Fisher exact test when expected numbers were
243 lower than 2.5. Significance level was considered at 0.05. The mapping was managed by the software
244 QGIS 2.14.

245 3. Results

246 3.1 Studies characteristics

247 3.1.1 Bibliometric analyses

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

255 The studies retrieved were:

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

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

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

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

277 3.1.2 Use and evaluation reports

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

279 Three hundred seventy seven ethnopharmacological survey use reports, corresponding to
280 264 species.

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

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

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

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

290 3.1.3 Geographical distribution

291 Fifty-eight articles originated from Africa, 35 articles from Asia and 18 articles from Latin America.
292 Regarding the number of species cited: 209 use reports were found in Africa (15 countries), 66 use
293 reports in Latin America (7 countries) and 222 use reports in Asia (8 countries). Most of the
294 publications included were carried out in India (n=23 articles), Nigeria (n=16), South Africa (n=13),
295 Cameroun and Brazil (n=8 each). Species were mainly recorded from India (196 different species),
296 Tanzania (81 of which 78 are different species), Belize (30 of which 21 are different), South Africa (28
297 different species) and Nigeria (22 different species). The distribution of species use reports across the
298 world is shown in Figure 2. Although most of the publications were either ethnopharmacological or
299 epilepsy models studies, we noted that only one Central American country (Belize) accounted both
300 ethnopharmacological studies and preclinical studies in equal proportion (15 reports from each). The
301 repartition of ethnopharmacological studies and preclinical trials by continents is presented in Table
302 1.

303 3.2 Ethnopharmacological and pharmacological approaches

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

306 3.2.1 Ethnopharmacological studies

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

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

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

326 3.2.2 Pharmacological studies

327 Among 149 evaluation reports of species (120 species evaluated on models and 29 evaluated on both
328 models and ethno pharmacology methods) recorded for *in vitro* and *in vivo* models, 41 species were
329 assessed on *in vitro* models, 91 on *in vivo* models and 17 were completely screened (both *in vitro* and
330 *in vivo* models). Species have been assessed on several biological models of epilepsy (Figure 3 and
331 Table 3). *In vivo* models were mainly used (81.6% of the total numbers of models). *In vitro* model
332 mostly used was the cerebral cortex bond-test GABA-A, with 55.2% of use reports. *In vivo* model
333 mostly applied was the injection of pentenyltetrazole (34.9%), followed by maximal electroshock
334 seizures (19.8%) and strychnine (16.7%). In Latin America, *in vitro* studies were most common
335 (60.0%) whereas in Asia and Africa, *in vivo* studies were more frequent (respectively 76.0 and 58.1%).
336 Ethanolic extracts were mainly used for *in vitro* studies whereas *in vivo* studies used aqueous,
337 ethanolic, organic extracts (ether or dichloromethane extracts), or both types. Extracts were
338 administered by intra-peritoneal route for 67.0% and other administrations were performed by oral
339 route. More than 66.7% of preclinical trials did not involve toxicity studies and 21 studies (30.4%) did
340 not use any positive control (AEDs) to compare efficacy with plant extracts. Only 20 studies (29.0%)
341 could be considered as high quality studies respecting criteria described in the Guidelines for
342 submission in peer-reviewed pharmacological literature (Mullane, Enna, Piette, & Williams, 2015).

343 3.3 Herbal remedies information

344 3.3.1 Botanical information

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

350 The species most cited was *Acorus calamus* L. (12 use reports and 2 evaluation reports), mentioned
351 both in surveys and in biological assays (pentenyltetrazole (PTZ) and maximal electroshock (MES)
352 models). *Bacopa monnieri* (L.) Wettst. was cited 8 times in four ethnopharmacological surveys and in
353 2 *in vivo* assays (extracts provided EEG protection as diazepam). *Leonotis leonurus* (L.) R.Br. (4
354 evaluation reports), *Uncaria Rhynchophylla* (Miq.) Miq. ex Havil., *Calotropis gigantea* (L.) Dryand. (3
355 evaluation reports each) had the greatest number of preclinical evaluation. *Ricinus communis* L.,
356 *Asparagus racemosus* Willd. and *Rauvolfia serpentina* (L.) Benth. ex Kurz were mentioned five times
357 in total (4 use reports and 1 evaluation report).

358 3.3.2 Medicinal species use

359 Parts of species used were mainly leaves in Africa (39.2%) and Latin America (51.2%). In Asia, roots
360 were mainly used (24.1%) and we also observed in this continent a great number of others parts as
361 fruits, rhizomes, bulbs, flowers, seeds and resins. There was a significant difference for the
362 repartition of species parts by continents as shown in Table 6 (p<0.001). For the mode of
363 preparation, we noted decoction was mainly used in Africa (54.7%) and Latin America (38.2%). In
364 Asia, the use of dry powders (22.6%) was the most common, followed by decoction (20.5%). We
365 observed a wider variety of preparation modes in Asia with also an important proportion of healers
366 who made maceration, extraction and paste. Other modes of preparation mentioned were juice,
367 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 peroxidized lipids
394 (participating in oxidative damages) (4 evaluation reports), AMPA receptor binding (2 evaluation
395 reports), enhancement of the serotonergic 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.

451 4.2 Distribution of the studies

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

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

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

475 4.3 Cultural beliefs related to epilepsy

476 Shorvon and Farmer (1988) gathered sociocultural studies in developing countries to report the
477 perceived causes of epilepsy; supernatural beliefs (e.g. breaking of taboo, visiting dangerous places),
478 environmental factors (e.g. climate, phases of the moon), physical ailments (e.g. malaria, bang on the
479 head or other accidents) and psychological determinants (e.g. anger, guilt, anxiety) were mentioned
480 in Africa (Nigeria, Kenya), Asia (India), and Latin America (Ecuador). The Latin American people
481 distinguished different types of epileptic seizures; the great evil was described as "heartbeat" and
482 "becoming cold". The symptoms of the little evil were "the vision that is darkening" and a "behavioral
483 cessation". Finally, the "explosive madness" seemed to describe the complex partial crises. In many
484 countries, the etiology of the disease was explained by mystical causes; it is the result of punishment
485 of the gods or deceased ancestors (Burneo, 2003). In a study conducted in Peru, epilepsy was
486 perceived as being caused by emotional problems (25% of cases), neurocysticercosis (18%), heredity
487 and witchcraft for respectively 16 and 15% of persons with epilepsy (PWE) surveyed (Auditeau et al.,
488 2018). More recently in Asia, a majority of PWE didn't know the etiology of their disease (18% of use
489 reports), followed by cranial traumatism (16%) and fever (14%). This wide variety of beliefs can be
490 correlated with the high diversity of therapeutic remedies used, which are discussed in
491 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 serpentina* (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 Sinai 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 peroxidized 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 Ethanol extracts were protective against seizures. No toxicity studies were available in the papers

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

629 *Asparagus racemosus* Willd. (Asparagaceae)

630 *Asparagus racemosus* Willd. is a wild herbaceous widely distributed in pantropical regions. Data from
631 four ethnopharmacological studies were collected and one study assessed both use reports by
632 communities and *in vivo* anticonvulsant activity of the species. One study reported other activity on
633 the central nervous system (inducing paralysis). Roots and rhizomes were used in the care of epilepsy
634 seizures in three Indian communities (Mallik et al., 2012; J. Sharma et al., 2013; U. K. Sharma et al.,
635 2012). Decoction of roots was used in one community, while in another village the dry powder and
636 the juice were consumed. Oral route was employed in all cases. The powder and decoction were
637 taken twice a day during one month. Five quantitative indicators, the UV, the FL, the relative
638 frequency of use reports, the relative importance and the cultural index were mentioned. Surveys
639 with 91 traditional healers of 3 different communities, formal interviews with local population and
640 elder people (J. Sharma et al., 2013); as well as surveys with traditional healers, village chiefs,
641 religious healers, PWE and housewives (Mallik et al., 2012); and semi-structured interviews with 84
642 informants (village chiefs, traditional healers, religious healers, farmers between 45 and 70) (U. K.
643 Sharma et al., 2012) were performed for ethnopharmacological studies. In the *in vivo* study,
644 methanolic and aqueous root extracts were assessed on pentenyltetrazole and maximal electroshock
645 seizures. Extracts provided protection against seizures. No toxicity studies were available in the
646 papers reviewed, and most of the toxicological studies performed on *Asparagus racemosus* Willd.
647 proved the long-term safety of the species (Singh et al., 2016). Further studies should be carried out
648 to better understand its mechanism of action in the treatment of epilepsy seizures.

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

650 *Rauvolfia serpentina* (L.) Benth. ex Kurz is a tropical cultivated shrub. Data from four
651 ethnopharmacological studies were collected and one study assessed both use reports by
652 communities and *in vivo* anticonvulsant activity of the species. One study reported other activities on
653 the central nervous system (nervous disorders, insomnia treatment and anti-venomous). Powder of
654 roots were used in the care of epilepsy seizures in five Indian communities (Poonam & Singh, 2009; J.
655 Sharma et al., 2013). Oral route was employed twice a day. Three quantitative indicators, UV, FL and
656 percentage of use reports were mentioned. Questionnaires with 91 traditional healers, priests,
657 women, farmers, elder people and inhabitants (Poonam & Singh, 2009); as well as observations and
658 focus group with elder people, traditional healers and people who have knowledge about plants of
659 60 villages (J. Sharma et al., 2013) were performed for ethnopharmacological studies. In an *in vivo*
660 study, aqueous extract was assessed on pentenyltetrazole and strychnine models. Extracts provided
661 protection against seizures. No toxicity studies were available in the papers reviewed. *Rauvolfia*
662 *serpentina* (L.) Benth. ex Kurz contains the famous active compound reserpine which was discovered
663 from this species in 1952. Although it has been proven to possess anticonvulsant activity in humans,

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

666
667 The use convergence was not frequent; only 2 species were reported more than 10. This could be
668 partly explained by the wide area studied and the difference of ecosystems between the countries.
669 Interestingly, within the same study area (rural communities in Peru), we observed a high use
670 convergence of some widespread plants as *Valeriana officinalis* L., *Myristica fragrans* Houtt. and
671 *Melissa officinalis* L. (Auditeau et al., 2018). These plants, which are not endemic to Peru, could be
672 used because of a real effectiveness was observed. In this context, it will be interesting to provide
673 pharmacological evaluation of these species in order to, if a pharmacological activity is
674 demonstrated, raise awareness and establish training activities for traditional healers which are more
675 often the first local actors consulted in case of epilepsy (60.5% of PWE in Peru had already used
676 herbal remedies for the care of epilepsy).

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

682

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 MTL 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.

724 5. Conclusion

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

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

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

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

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

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

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

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

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

759 Finally, it will be interesting to provide new models of epileptogenesis, in particular to study epilepsy
760 associated with parasites and inflammation (Nash et al., 2015), as neurocysticercosis, to understand
761 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
788 there has been no significant financial support for this work that could have influenced its outcome.

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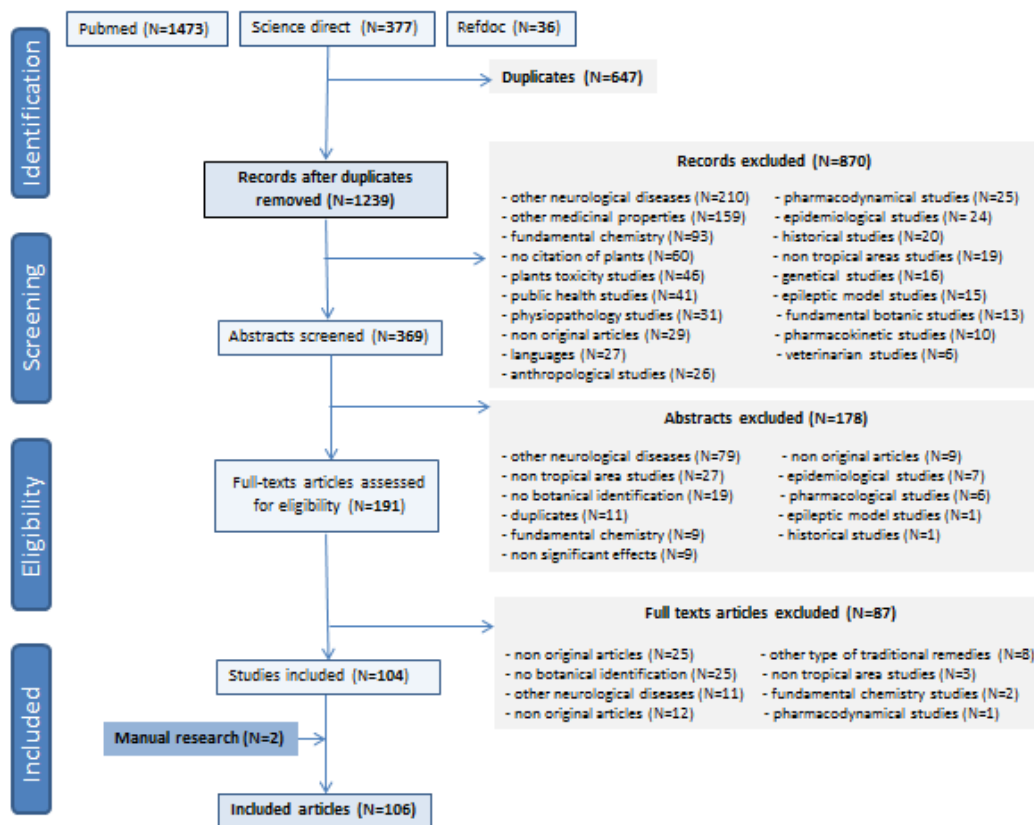


Figure 1: Flow-chart of the literature review

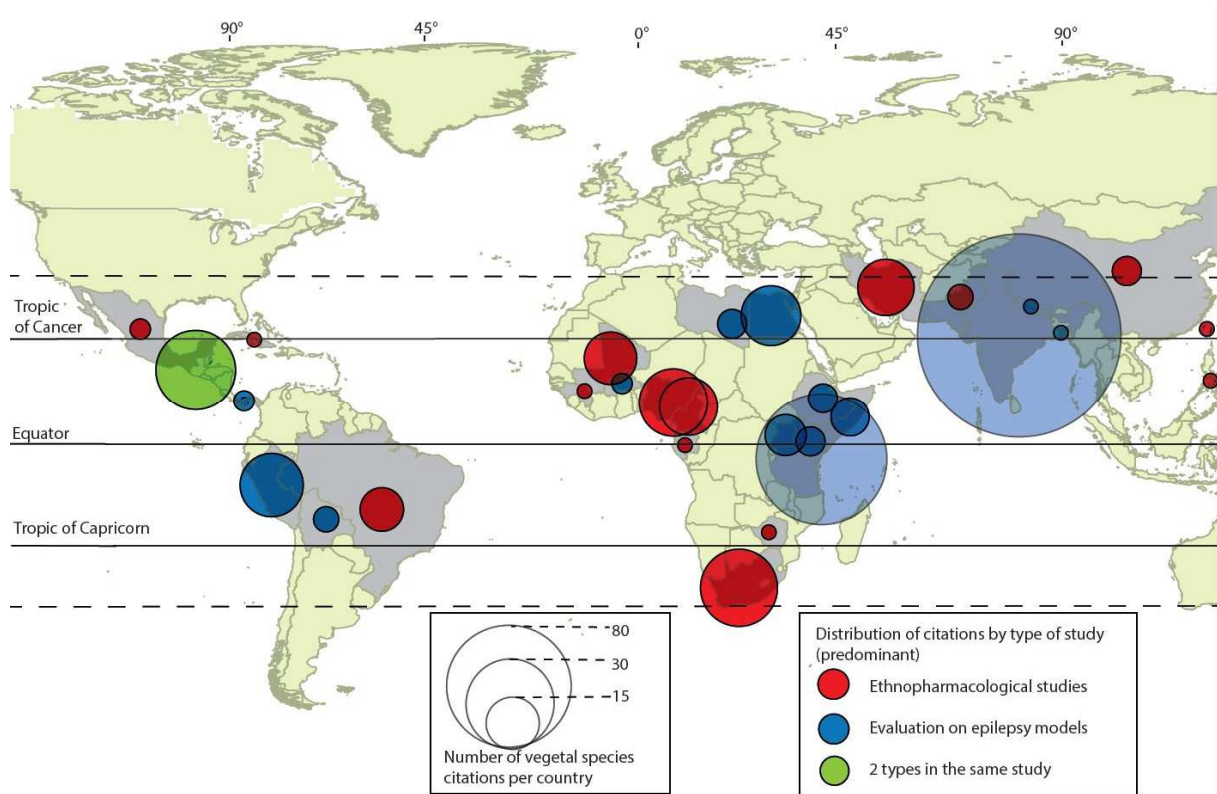


Figure 2: Distribution of plant species use reports by country and type of study

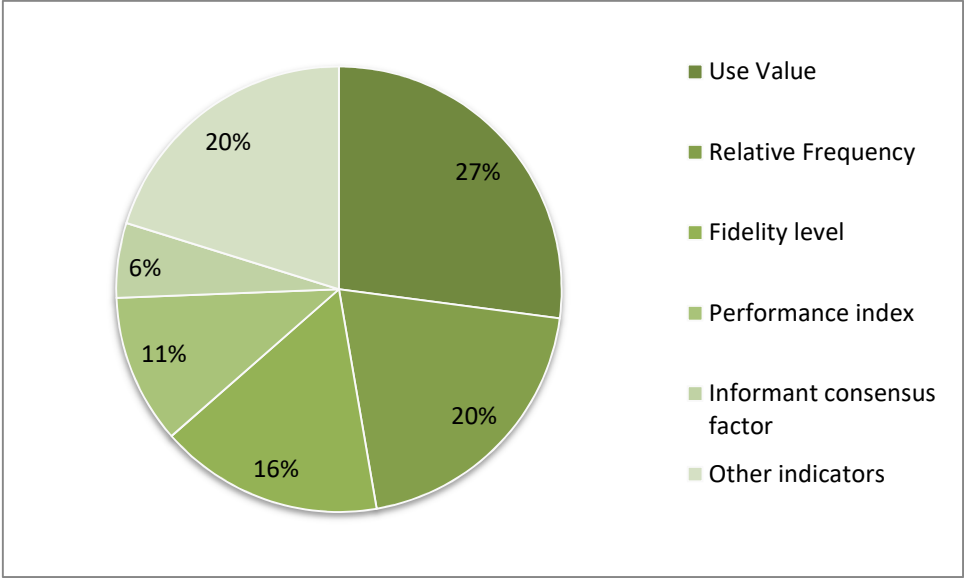


Figure 3: Repartition of quantitative indicators for ethnopharmacological studies

Table 1. Repartition of study type by continents

	Ethnopharmacological studies		Epilepsy models		p
	Number	Frequency (%)	Number	Frequency (%)	
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	<0.001	2	25	3	<0.001
Asia	49	26.6		27	9	13	
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
<i>In vitro models</i>		
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
<i>In vivo models</i>		
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	Countries	Part of specie	Traditional preparation way	Administration	Doses	Informants	Sample size	Type of survey	Study period	Results	Reference
<i>Carissa spinarum</i> 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
<i>Culcasia falcifolia</i> Engl.	Araceae		Leaves	Ash								
<i>Ehretia cymosa</i> Thonn.	Boraginaceae		Leaves and root	Infusion								
<i>Solanecio manni</i> (Hook.f.) C.Jeffrey	Asteraceae		Roots	Decoction								
<i>Achyranthes aspera</i> 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	-	<i>Achyranthes aspera</i> : 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 <i>Evolvulus alsinoides</i> : Plant with a very good effectiveness in epilepsy for the 4 tribes, not known in this indication by traditional practitioners	Kumar et al., 2004
<i>Evolvulus alsinoides</i> (L.) L.	Convolvulaceae		Whole plant	Paste		1/day during 1 month						
<i>Euphorbia dracunculoides</i> 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
<i>Gomphrena celosioides</i> Mart.	Amaranthaceae		Leaves	Juice								
<i>Ocimum gratissimum</i> L.	Polygalaceae		Leaves	Paste								
<i>Oxalis corniculata</i> L.	Oxalidaceae		Leaves	Pulverization								

Species	Family	Countries	Part of specie	Traditional preparation way	Administration	Doses	Informants	Sample size	Type of survey	Study period	Results	Reference
<i>Allium cepa</i> 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
<i>Aristolochia indica</i> L.	Aristolochiaceae	India	Roots	Juice	In the nose	-	Traditional healers	-	-	-	Traditional medicine use in India	Pushpangadan et al., 1984
<i>Ipomoea eriocarpa</i> R. Br.	Convolvulaceae		Whole plant	Extraction	With honey							
<i>Glycosmis pentaphylla</i> (Retz.) DC.	Rutaceae		Whole plant	Juice	PO or on the head							
<i>Euphorbia tirucalli</i> L.	Euphorbiaceae	Somalia	Aerial parts	-	-	-	Traditional healers	-	-	-	Traditional medicine use in Somalia	Samuelsson et al., 1992
<i>Jatropha curcas</i> L.	Euphorbiaceae		Roots	-	-							
<i>Flueggea virosa</i> (Roxb. ex Willd.) Royle	Phyllanthaceae		Leaves	Juice	PO							
<i>Launaea cornuta</i> (Hochst. ex Oliv. & Hiern) C. Jeffrey	Compositae		Leaves and roots	Decoction	-							
<i>Cullen corylifolium</i> (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
<i>Dichrostachys cinerea</i> (L.) Wight & Arn.	Mimosaceae		-	Decoction								
<i>Indigofera tinctoria</i> L.	Leguminosae		Leaves	Juice and decoction								
<i>Baccharoides lasiopus</i> (O. Hoffm.) H. Rob.	Compositae	Tanzania	Leaves	Decoction	-	-	Traditional healers	114	-	November to December 1978 and 1979	Traditional medicine use in Tanzania for children (<i>Conyza pyrrhopappa</i> , <i>Markhamia obtusifolia</i> , <i>Senna singueana</i> ,	Hedberg et al., 1982
<i>Conyza pyrrhopappa</i> Sch. Bip. ex A. Rich	Compositae		Roots	Decoction	-							
<i>Gymnanthemum coloratum</i> (Willd.) H. Rob. & B. Kahn	Compositae		Leaves and inflorescence	Infusion	Inhalation							
<i>Gymnosporia heterophylla</i> (Eckl. &	Celastraceae		Roots	Decoction	PO							

Species	Family	Countries	Part of specie	Traditional preparation way	Administration	Dose	Informants	Sample size	Type of survey	Study period	Results	Reference
<i>Catunaregam nilotica</i> (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 (<i>Hoslundia opposita</i> , <i>Grewia forbesii</i> and <i>Waltheria indica</i>) and adults for other plants	Hedberg et al., 1983
<i>Crossopteryx febrifuga</i> (Afzel. ex G.Don) Benth.	Rubiaceae		Leaves and bark of roots	Pulverization and juice	-							
<i>Grewia forbesii</i> Harv. ex Mast.	Tiliaceae		Roots	Decoction	-							
<i>Solanum incanum</i> L.	Solanaceae		Fruit	Paste	-							
<i>Waltheria indica</i> L.	Malvaceae		Leaves and roots	Decoction	Inhalation and PO							
<i>Dichrostachys cinerea</i> (L.) Wight & Arn.	Mimosaceae		-	Decoction	-							
<i>Flueggea virosa</i> (Roxb. ex Willd.) Royle	Phyllanthaceae		Leaves	Juice	PO							
<i>Hoslundia opposita</i> Vahl	Lamiaceae		Roots	Decoction	-							
<i>Curculigo orchoides</i> Gaertn.	Amaryllidaceae	India	Roots	Paste	-	-	Local and community elders	-	-	1998 to 2001	Traditional medicine use in India	Singh et al., 2002
<i>Evolvulus alsinoides</i> (L.) L.	Convolvulaceae		Leaves	Paste	-							
<i>Justicia ephemera</i> Leonard	Acanthaceae	Panama	Whole plant	-	On chest and arms	-	Native informants with traditional healers help, Traditional healers	-	-	-	Traditional medicine use in Panama for children (<i>Justicia ephemera</i>) Traditional medicine use in Panama and Egypt too (<i>Sapindus saponaria</i>)	Gupta et al., 1993
<i>Sapindus saponaria</i> L.	Sapindaceae		-	Infusion	-							
<i>Sesbania grandiflora</i> (L.) Pers.	Leguminosae	Bangladesh	Fresh leaves	Juice with <i>piper nigrum</i>	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
<i>Capparis tomentosa</i> 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	Countries	Part of specie	Traditional preparation way	Administration	Doses	Informants	Sample size	Type of survey	Study period	Results	Reference
<i>Artemisia nilagirica</i> (C.B.Clarke) Pamp.	Compositae	India	Leaves	Infusion	-	-	Elders, traditional healers	-	-	2000 to 2002	Traditional medicine use in India	Sharma et al., 2004
<i>Acorus calamus</i> L.	Araceae		-	-	-							
<i>Cannabis sativa</i> L.	Cannabaceae		-	-	-							
<i>Cissampelos pareira</i> L.	Menispermaceae		-	-	-							
<i>Nardostachys jatamansi</i> (D.Don) DC.	Valerianaceae		Roots	-	-							
<i>Helichrysum setosum</i> Harv.	Compositae	Tanzania	Leaves	Decoction	PO	-	Traditional healers	-	-	-	Traditional medicine use in Tanzania	Chhabra et al., 1984
<i>Uvaria leptocladon</i> Oliv.	Annonaceae		Leaves and young growths	Decoction	-	-						

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

Species	Family	Countries	Part of specie	Traditional preparation way	Administration	Doses=	Informants	Sample size	Type of survey	Study period	Results	Reference
<i>Bactris gasipaes</i> 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
<i>Costus productus</i> Gleason ex Maas	Zingiberaceae		Leaves	Infusion	Bath	-						
<i>Dichorisandra hexandra</i> (Aubl.) Standl.	Commeliaceae		Flowers	Juice	Ocular instillation	one drop						
<i>Elaphoglossum cuspidatum</i> (Willd.) T. Moore	Lomariopsidaceae		Leaves	Infusion	Bath	-						
<i>Elaphoglossum megalurum</i> Mickel	Lomariopsidaceae		Leaves	Infusion	Bath	1/day						
<i>Elaphoglossum raywaense</i> (Jenman) Alston	Lomariopsidaceae		Leaves	Infusion	Bath	1/day						
<i>Acacia amythethophylla</i> 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
<i>Acacia seyal</i> Delile	Leguminosae		Roots	Pulverization	PO, bath, topic							
<i>Carissa spinarum</i> L.	Apocynaceae		Roots	Pulverization	PO, bath, topic							
<i>Combretum collinum</i> Fresen.	Combretaceae		Roots	Pulverization	PO, bath, topic							
<i>Kalanchoe densiflora</i> Rolfe	Crassulaceae		Leaves: sap	Extraction and infusion	PO, eye, navel instillation							
<i>Oncoba spinosa</i> Forsk.	Flacourtiaceae		Roots	Pulverization	PO, inhalation							
<i>Terminalia glaucescens</i> Planch. ex Benth.	Combretaceae		Roots	Pulverization	PO, bath, topic							
<i>Asparagus racemosus</i> 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

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

Species	Family	Countries	Part of specie	Traditional preparation way	Administration	Doses	Informants	Sample size	Type of survey	Study period	Results	Reference
<i>Euclea racemose</i> 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
<i>Withania somnifera</i> (L.) Dunal	Solanaceae		Roots	Decoction	PO							
<i>Cascabela thevetia</i> (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
<i>Ambrosia peruviana</i> Willd.	Compositae		Leaves, stem	Decoction	PO	-						
<i>Lonicera japonica</i> Thunb.	Caprifoliaceae		Whole plant	Decoction	PO	3-4 cup/day during 2-3 months						
<i>Cassia fistula</i> L.	Leguminosae		Seeds	Maceration	PO	1 cup/day during 15-20 days						
<i>Myroxylon balsamum</i> (L.) Harms	Leguminosae		Seeds	Juice	PO	3 little cup/day						
<i>Tamarindus indica</i> L.	Leguminosae		Fruit	Decoction	PO	1 glass/day during 30 days						
<i>Aiouea dubia</i> (Kunth) Mez	Lauraceae		Seeds	Decoction, bath	PO, bath	1/month						
<i>Ocotea floribunda</i> (Sw.) Mez	Lauraceae		Seeds, leaves, flowers	Decoction	PO	Decoction: 1L/day 7 to 15 days Limpia: 3 times a week						
<i>Malva sylvestris</i> L.	Malvaceae		Leaves, stem	Decoction	PO	1L/day during 15 days						
<i>Myristica fragrans</i> Houtt.	Myristicaceae		Seeds	Decoction	PO	1/month						
<i>Peperomia inaequalifolia</i> Ruiz & Pav.	Piperaceae		Whole plant	Inhalation	PO, inhalation	3-4/day during 1-2 months						
<i>Laccopetalum giganteum</i> (Wedd.) Ulbr.	Renonculaceae		-	Decoction	PO	1-2 cup/day during 25 days						
<i>Viola tricolor</i> 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	Countries	Part of specie	Traditional preparation way	Administration	Doses	Informants	Sample size	Type of survey	Quantification of use	Study period	Results	Reference
<i>Acorus calamus</i> 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%	Sharma et al., 2013
<i>Allium sativum</i> L.	Amaryllidaceae		Bulb	Decoction		half-cup							
<i>Asparagus racemosus</i> Willd.	Asparagaceae		Roots	Powder		2g 2/day for 2-3 weeks							
<i>Bacopa monnieri</i> (L.) Wettst.	Plantaginaceae		Leaves	Paste, juice, decoction		2 or 3/day							
<i>Boerhavia diffusa</i> L.	Nyctaginaceae		Roots	Powder		3g							
<i>Calotropis gigantea</i> (L.) Dryand.	Apocynaceae		Bark	Decoction		1s 2/day for 2weeks							
<i>Datura stramonium</i> L.	Solanaceae		Fresh leaves and roots	Decoction		2/day							
<i>Oxalis corniculata</i> L.	Oxalidaceae		Whole plant	Decoction		2s							
<i>Punica granatum</i> L.	Punicaceae		Leaves	Decoction		half-cup							
<i>Rauvolfia serpentina</i> (L.) Benth. ex Kurz	Apocynaceae		Roots	Decoction		1g, 2/day							
<i>Ricinus communis</i> L.	Euphorbiaceae		Leaves	Infusion		-							
<i>Vitex negundo</i> L.	Verbenaceae		Roots	Powder		1-2s 1-2/day							
<i>Dicerotheramnus rhinocerotis</i> (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
<i>Dodonaea viscosa</i> (L.) Jacq.	Sapindaceae		Leaves	Infusion		3/day							

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

Species	Family	Countries	Part of specie	Traditional preparation way	Administration	Doses	Informants	Sample size	Type of survey	Quantification of use	Study period	Results	Reference
<i>Artemisia vulgaris</i> L.	Compositae	Bolivia	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
<i>Dianthus caryophyllus</i> L.	Caryophyllaceae		Flowers	Infusion									
<i>Franseria artemisioides</i> Willd.	Compositae		Roots	Infusion									
<i>Bacopa monnieri</i> (L.) Wettst.	Plantaginaceae	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 December 2007	Frequencies of use : 41% 45% 41% 44% 29% 23% Traditional medicine use in India	Poonam et al., 2009
<i>Curculigo orchioides</i> Gaertn	Amaryllidaceae		Roots	Pulverization		2 s 2/day							
<i>Cynodon dactylon</i> (L.) Pers.	Poaceae		Whole plant	Infusion		50 ml 2/day							
<i>Evolvulus Alsinooides</i> (L.) L.	Convolvulaceae		Whole plant	Juice		2-3 s 2/day							
<i>Plectranthus amboinicus</i> (Lour.) Spreng.	Lamiaceae		Leaves	Juice		1 s 2/day							
<i>Rauvolfia serpentina</i> (L.) Benth. ex Kurz	Apocynaceae		Roots	Pulverization		1-2 s 2/day							
<i>Allium cepa</i> L.	Amaryllidaceae		Nigeria	Bulb		Pulverization							
<i>Jatropha curcas</i> L.	Euphorbiaceae	Leaves		Pulverization									
<i>Ricinus communis</i> L.	Euphorbiaceae	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%	Purkayastha et al., 2005

Species	Family	Countries	Part of specie	Traditional preparation way	Administration	Dose	Informants	Sample size	Type of survey	Quantification of use	Study period	Results	Reference
<i>Anastatica hierochuntica</i> L.	Brassicaceae	Egypt	Whole plant, fruit	Decoction	PO (for all the plants)	-	Men aged 49 to 69	700	Interviews with semi-structured questionnaires	I/P (number of interview / number of inhabitants) 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 : 0,05 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	Eissa et al., 2013
<i>Bacopa monnieri</i> (L.) Wettst.	Plantaginaceae		Aerial parts	Infusion									
<i>Citrullus colocynthis</i> (L.) Schrad.	Cucurbitaceae		Fruit	-									
<i>Datura stramonium</i> L.	Solanaceae		Aerial parts	Infusion									
<i>Ferula sinaica</i> Boiss.	Apiaceae		Roots	Maceration									
<i>Globularia arabica</i> Jaub. & Spach	Globulariaceae		Whole plant	Infusion									
<i>Haplophyllum vermiculare</i> Hand.-Mazz	Rutaceae		Leaves	Infusion									
<i>Lavandula pubescens</i> Decne	Lamiaceae		Flowers	Infusion									
<i>Leontice leontopetalum</i> L.	Leonticaceae		Roots	Infusion									
<i>Melilotus indicus</i> (L.) All.	Leguminosae		Aerial parts, flowers, seeds	Infusion									
<i>Peganum harmala</i> L.	Zygophyllaceae		Leaves	Infusion									
<i>Pluchea dioscoridis</i> (L.) DC.	Compositae		Aerial parts, leaves	Juice									
<i>Ruta graveolens</i> L.	Rutaceae		Leaves	Infusion									
<i>Salvia multicaulis</i> Vahl	Lamiaceae		Leaves	Infusion									
<i>Solenostemma argel</i> (Delile) Hayne	Asclepiadaceae		Leaves	Infusion									
<i>Teucrium leucocladum</i> Boiss.	Lamiaceae	Leaves	Infusion										
<i>Teucrium polium</i> L.	Lamiaceae	Whole plant	Decoction										

Species	Family	Countries	Part of specie	Traditional preparation way	Administration	Dose	Informants	Sample size	Type of survey	Quantification of use	Study period	Results	Reference
<i>Adelobotrys adscendens</i> (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	Awad et al., 2009
<i>Adiantum latifolium</i> Lam.	Adiantaceae		RF>0.333										
<i>Adiantum princeps</i> T. Moore	Adiantaceae		RF>0.333										
<i>Adiantum tetraphyllum</i> Humb. & Bonpl. ex Willd.	Adiantaceae		RF>0.333										
<i>Adiantum wilsonii</i> Hook.	Adiantaceae		RF<0.333										
<i>Aristolochia grandiflora</i> Sw.	Aristolochiaceae		RF>0.333										
<i>Gonzalagunia rosea</i> Standl.	Rubiaceae		RF>0.333										
<i>Justicia albobracteata</i> Leonard	Acanthaceae		RF>0.333										
<i>Justicia aurea</i> Schltld.	Acanthaceae		RF<0.333										
<i>Justicia pectoralis</i> Jacq.	Acanthaceae		RF>0.333										
<i>Lygodium heterodoxum</i> Kunze	Schizaeaceae		RF<0.333										
<i>Lygodium venustum</i> Sw.	Schizaeaceae		RF>0.333										
<i>Petiveria alliacea</i> L.	Phytolaccaceae		RF>0.333										
<i>Piper amalago</i> L.	Piperaceae		RF<0.333										
<i>Piper tuerckheimii</i> C.DC	Piperaceae		RF>0.333										
<i>Pityrogramma calomelanos</i> (L.) Link	Adiantaceae		RF<0.333										
<i>Porophyllum ruderale</i> (Jacq.) Cass.	Compositae	RF>0.333											
<i>Baccharis inamoena</i> Gardner	Compositae	RF<0.333											
												Relative frequency>0.033 signifies a high traditional medicine use	

<i>Psychotria tenuifolia</i> Sw.	Rubiaceae												
<i>Selaginella stellate</i> Spring	Selaginellac eae												
<i>Stachytarpheta frantzii</i> Pol.	Verbenacea e												
<i>Moringa oleifera</i> Lam.	Moringaceae	Nigeria	Leaves and bark	Decoction	PO	-	60% men	745	Face-to- face interview s, semi- structure d question naires	Fidelity level	March 2011 to Januar y 2013	FL : 70 % Traditional medicine and other uses in Nigeria	Popoola et al., 2013

Species	Family	Countries	Part of specie	Traditional preparation way	Administration	Doses	Informants	Sample size	Type of survey	Quantification of use	Study period	Results	Reference
<i>Inula cappa</i> (Buch.-Ham. ex D.Don) DC.	Compositae	Nepal	Roots	Juice	PO	-	Men and women, including 2 traditional practitioners and 3 elders	62	Structured questionnaires and discussion with villagers	Frequency of citations	August to December 2000	Frequency of citations : 9.7 % Traditional medicine use in Nepal	Shrestha et al., 2003
<i>Calotropis procera</i> (Aiton) Dryand.	Asclepiadaceae	Burkina Faso	Roots	Pulverization, maceration, decoction	-	-	Traditional healers (aged 35 to 76)	41	Semi-structured interviews	Number of citations	May to September 2007 and 2008	Number of citations : 15 for both plants Traditional medicine use in Burkina Faso	Nadembega et al., 2011
<i>Combretum micranthum</i> G.Don	Combretaceae		Leaves, branches	Maceration									
<i>Parkinsonia aculeata</i> L.	Cesalpiniaceae	Brazil	Bark, roots, flowers, sedes, raffia	-	-	-	-	-	-	RI (relative importance), NCS (number of body system treated), NP (number of pharmacological properties)		RI : 1.2 RI > 1: widely used plant and she has many other pharmacological characteristics Traditional medicine use in Brazil	De Albuquerque et al., 2007
<i>Asparagus racemosus</i> Willd.	Asparagaceae	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 questionnaires	RFC (relative frequency of citation), RI (relative importance), CI (cultural index)	January 2009 to June 2011	<i>Asparagus racemosus</i> RFC: 0.36 / RI: 0.34/ CI: 0.12 <i>Citrus maxima</i> RFC: 0.14 / RI: 0.32 RI<0.5: low used plant in India	Sharma et al., 2012
<i>Citrus maxima</i> (Burm.) Merr.	Rutaceae		Leaves, fruit	Extraction									
<i>Mikania glomerata</i> Spreng.	Compositae	Brazil	-	-	-	-	-	-	-	RI (relative importance)	-	RI: 0.84 Moderated traditional medicine use in Brazil	Medeiros et al., 2013

Species	Family	Countries	Part of specie	Traditional preparation way	Administration	Doses	Informants	Sample size	Type of survey	Quantification of use	Study period	Results	Reference
<i>Adiantum latifolium</i> 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
<i>Adiantum princeps</i> T. Moore	Adiantaceae			Maceration									
<i>Adiantum tetraphyllum</i> Humb. & Bonpl. ex Willd.	Adiantaceae			Maceration									
<i>Adiantum wilsonii</i> Hook.	Adiantaceae			Maceration									
<i>Aristolocha grandiflora</i> Sw.	Aristolochiaceae			Maceration and decoction									
<i>Justicia aurea</i> Schtdl.	Acanthaceae			Maceration									
<i>Lygodium heterodoxum</i> Kunze	Schizaeaceae			Maceration									
<i>Lygodium venustum</i> Sw.	Schizaeaceae			Maceration									
<i>Selaginella stellata</i> Spring	Selaginellaceae			Maceration and decoction									
<i>Allium cepa</i> L.	Amaryllidaceae	India	Bulb	Paste (for all the plants)	Inhalation / 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
<i>Allium sativum</i> L.	Amaryllidaceae		Bulb										
<i>Cinnamomum camphora</i> (L.) J.Presl	Lauraceae		Leaves										
<i>Ferula assa-foetida</i> L.	Apiaceae		Oleo-resin										

<i>Nicotiana glauca</i> Graham	Solana ceae	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
<i>Pteronia camphorata</i> (L.) L.	Compo sitae		Leaves	Dry powder									
<i>Limeum africanum</i> L.	Mollugi naceae		-	Decoction									

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
<i>Ajuga integrifolia</i> Buch.-Ham.	Lamiaceae	Ethiopia	Leaves	Pulverization and mix with nut oil	PO	-	Traditional practitioners (men and women) and community members	195	Field observatio ns, semi- structured interviews	Fidelity level (FL)		High fidelity level Traditional medicine use in Ethiopia	Woldeama nuel 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		p
	Number	Frequency (%)	Number	Frequency (%)	Number	Frequency (%)	
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							
<i>Per os</i>	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	Countries	Part of specie	Preparation way	Type of models	Name of models	Extracts	Administration	Doses (mg/kg)	Gold standard	Observed criteria	Toxicity	Results	Reference
<i>Gastrodia elata</i> Blume	Orchidaceae	China	Roots	Infusion	<i>In vivo</i> & <i>in vitro</i>	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. <i>In vitro</i> : ↑ GABA / inhibition GABA transaminase / Inhibitor effect of lipid peroxidation	Ha et al., 2010
<i>Arctopus echinatus</i> L.	Apiaceae	South Africa, Zimbabwe	Roots	Decoction, juice	<i>In vitro</i>	3H-Ro binding test	Ethanollic	-	-	Diazepam	Link to the GABA-A receptor	-	Significant liaison	Stafford et al., 2015
<i>Cotyledon orbiculata</i> L.	Crassulaceae		Leaves	Decoction, juice										
<i>Artemisia afra</i> Jacq. ex Willd.	Compositae		Leaves	Decoction, juice										
<i>Dioscorea dregeana</i> (Kunth) T.Durand & Schinz	Dioscoreaceae		Leaves	Decoction, juice										
<i>Acacia sieberiana</i> DC.	Leguminosae		Bark	Decoction, juice										
<i>Vitex negundo</i> L.	Verbenaceae	India	Leaves	Maceration	<i>In vivo</i>	MES, PTZ	Ethanollic	PO	250, 500 et 1000	Diphenylhydantoin, VPA	Duration extension phase	-	Potentiation : ↑ AE activity of VPA	Tandon et al., 2015
<i>Acorus calamus</i> L.	Araceae	India	-	-	<i>In vivo</i>	MES, PTZ	Methanolic, ethanollic, oil	PO	100 et 200	-	Intensity and duration of seizures	Mutagen Hepatocarcinogen	AE activity via GABA and sodium channel inhibition	Rajput et al., 2014
<i>Kalanchoe crenata</i> (Andrews) Haw.	Crassulaceae	Cameroon	Leaves	Maceration	<i>In vivo</i>	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	Countries	Part of specie	Preparation way	Type of models	Name of models	Extracts	Administration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference
<i>Tetrapleura tetraptera</i> (Schum. & Thonn.) Taub	Leguminosae	South Africa	Fruit	-	<i>In vivo</i>	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
<i>Delphinium denudatum</i> Wall. ex Hook.f. & Thomson	Renonculaceae	Pakistan	Roots	-	<i>In vivo</i>	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
<i>Leonotis leonurus</i> (L.) R.Br	Lamiaceae	South Africa	Leaves	Smoking	<i>In vivo</i>	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
<i>Benkara malabarica</i> (Lam.) Tirveng.	Rubiaceae	India	Roots	-	<i>In vivo</i> & <i>In vitro</i>	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
<i>Carissa spinarum</i> L.	Apocynaceae	Nigeria	Bark of roots	-	<i>In vivo</i> & <i>In vitro</i>	PTZ, MES, naloxone and flumazenil	Ethanollic	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
<i>Delphinium nordhagenii</i> Wendelbo	Renonculaceae	Pakistan	Aerial parts	-	<i>In vivo</i>	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
<i>Harpagophytum zeyheri</i> (Engl.) Ihlenf. & H.E.K.Hartmann	Pedaliaceae	South Africa	Roots	-	<i>In vivo</i>	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	Countries	Part of specie	Preparation way	Type of models	Name of models	Extracts	Administration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference
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<i>Erythrina verna</i> Vell.	Leguminosae	Brazil	Bark of trunk	-	<i>In vivo</i>	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
<i>Erythrina velutina</i> Willd.	Leguminosae		Bark of trunk						200, 400 mg/kg					
<i>Justicia extensa</i> T.Anderson	Acanthaceae	Nigeria	Leaves	-	<i>In vivo</i>	Strychnine, picrotoxin	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
<i>Valeriana officinalis</i> L.	Valerianaceae	Iran	Roots	-	<i>In vivo</i>	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
<i>Marsilea quadrifolia</i> L.	Marsileaceae	India	Whole plant	Maceration	<i>In vivo</i>	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
<i>Rhus chirindensis</i> Baker f.	Anacardiaceae	South Africa	Barks and stem	Decoction and infusion	<i>In vivo</i>	PTZ, bicuculline, picrotoxin	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
<i>Piper guineense</i> Schumacher & Thonn.	Piperaceae	Nigeria	-	Powder	<i>In vivo</i>	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	Countries	Part of specie	Preparation way	Type of models	Name of models	Extracts	Administration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference
<i>Magnolia grandiflora</i> L.	Magnoliaceae	Mexico	Seeds	-	<i>In vivo</i>	MES	Ethyl ether, hydroalcoholic	PO	10 à 1000 mg/kg	-	Percentage of protection against seizures, duration and latency of convulsions	Acute toxicity: no neurodeficiency	Effect on protection, latency and duration on recuperation of orthostatism and extension reflexes	Bastidas Ramirez et al., 1998
<i>Cyperus articulatus</i> L.	Cyperaceae	Cameroun	Rhizomes	Decoction	<i>In vivo</i>	PTZ, INH, pilocarpine, STN, isoniazid, bicuculline	Methanolic	IP	50 à 2000 mg/kg	Clonazepam, diazepam, carbamazepine	Protection against seizures	At doses of 1000 and 2000 mg/kg: ataxia 1h after administration	Dose dependent effect on PTZ and INH	Bum et al., 2001
<i>Securidaca longepedunculata</i> Fresen.	Polygalaceae	Nigeria	Roots	-	<i>In vivo</i>	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
<i>Sarcocephalus latifolius</i> (Sm.) E.A.Brucée	Rubiaceae	Cameroun	Bark, leaves, roots, fruit, stem	Decoction	<i>In vivo</i>	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	Countries	Part of specie	Preparation way	Type of models	Name of models	Extracts	Administration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference
<i>Albizia lebbek</i> (L.) Benth.	Mimosaceae	India	Leaves and bark	Decoction	<i>In vivo & in vitro</i>	MES, electrical kindling, PTZ, lithium, pilocarpine, STN	Ethanollic / ether petroleum/ethanollic	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
<i>Butea monosperma</i> (Lam.) Taub.	Leguminosae		Flowers and roots	Maceration					20 à 200 mg/kg					
<i>Hibiscus mutabilis</i> L.	Malvaceae		Flowers	Decoction					20 à 200 mg/kg					
<i>Gastrodia elata</i> Blume	Orchidaceae	China	-	-	<i>In vivo & in vitro</i>	Kainic acid	Alcoholic	PO	250, 500, 1000 mg/kg	Carbamazepine	Estimated peroxidized lipid level, percentage of protection against seizures, convulsions latency, EEG, EMG	-	Increase of peroxidized lipids (contribute to oxidative damage). Effect on protection against seizures and latency of seizures	Hsieh et al., 1999
<i>Uncaria Rhynchophylla</i> (Miq.) Miq. ex Havil.	Rubiaceae													
<i>Mondia whitei</i> (Hook.f.) Skeels	Apocynaceae	Nigeria	Leaves, roots	-	<i>In vivo</i>	Pilocarpine	Methanollic	-	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	Countries	Part of specie	Preparation way	Type of models	Name of models	Extracts	Administration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference
<i>Lobelia nicotianaefolia</i> Roth ex Schult.	Campanulaceae	India	Flowers, leaves, roots	-	<i>In vivo</i> & <i>in vitro</i>	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
<i>Viscum capense</i> L. f.	Loranthaceae	South Africa	Stems	-	<i>In vivo</i>	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
<i>Stylosanthes erecta</i> P.Beauv.	Leguminosae	Mali	Leaves, aerial parts	-	<i>In vitro</i>	GABA A binding study	Ethanollic / dichloro methane	IP	0,1, 10 mg/kg	-	Percentage of binding of flumazenil to GABA A receptor	-	Dose dependent binding to receptor GABA A	Bah et al., 2007
<i>Trichilia emetic</i> Vahl	Meliaceae		Roots, bark, leaves						0,1, 10 mg/kg					
<i>Viola betonicifolia</i> Sm.	Violaceae	Pakistan	Whole plant	-	<i>In vivo</i>	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
<i>Leonotis leonurus</i> (L.) R.Br.	Lamiaceae	South Africa	-	-	<i>In vivo</i>	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
<i>Waltheria indica</i> L.	Malvaceae	Guinea	Roots, stem	-	<i>In vivo</i>	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	Countries	Part of species	Preparation way	Type of models	Name of models	Extracts	Administration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference
<i>Bacopa monnieri</i> (L.) Wettst.	Plantaginaceae	India	Whole plant	Juice	<i>In vivo</i>	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
<i>Cyperus rotundus</i> L.	Cyperaceae		Bulbous roots	Decoction										
<i>Saussurea costus</i> (Falc.) Lipsch.	Compositae		Roots	Decoction										
<i>Calotropis gigantea</i> (L.) Dryand.	Apocynaceae	India	Roots, flowers, leaves, bark of the stem	Infusion	<i>In vivo</i>	MES, PTZ	Aqueous, petroleum ether, methanolic	PO	180, 200 mg/kg	Phenytoin	Percentage of protection against seizures	-	Effect on protection against seizures	Karkiet et al., 2010
<i>Calotropis gigantea</i> (L.) Dryand.	Apocynaceae	India	Roots	Infusion	<i>In vivo</i>	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
<i>Petiveria alliacea</i> L.	Phytolaccaceae	Brazil	Roots	-	<i>In vivo</i>	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
<i>Mentha aquatica</i> L.	Lamiaceae	South Africa	Aerial parts	-	<i>In vitro</i>	GABA binding	Ethanollic and essential oil	-	-	-	Percentage of binding to GABA A receptor	-	Low binding to receptor GABA A	Jäger et al., 2007
<i>Bridelia micrantha</i> (Hochst.) Baill.	Euphorbiaceae	Cameroun	Bark	Decoction	<i>In vivo</i>	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
<i>Croton macrostachyus</i> Hochst. ex Delile	Euphorbiaceae		Bark	Decoction					15 à 135 mg/kg					

Species	Family	Countries	Part of specie	Preparation way	Type of models	Name of models	Extracts	Administration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference
<i>Pericopsis laxiflora</i> (Baker) Meeuwen	Leguminosae	Nigeria	Roots	Decoction	<i>In vivo</i>	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
<i>Desmodium adscendens</i> (Sw.) DC.	Leguminosae	Gabon	Leaves	Decoction	<i>In vivo</i>	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
<i>Croton penduliflorus</i> Hutch.	Euphorbiaceae	Nigeria	Seeds	-	<i>In vivo</i>	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	Countries	Part of specie	Preparation way	Type of models	Name of models	Extract	Administration	Doses (mg/kg)	Gold standard	Observed criteria	Toxicity	Results	Reference
<i>Terminalia chebula</i> Retz.	Combretaceae	Iran	Fruit	-	<i>In vivo</i> & <i>in vitro</i>	In vivo: PTZ, MES, picrotoxicine, pilocarpine, STN, 4-aminopyridine	Hydroalcoholic (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	-	<p><i>Terminalia chebula</i> has an effect on mortality, duration and latency.</p> <p><i>Pimpinella anisum</i> is protective against tonic extension, mortality, increase the threshold and latency of convulsions and decrease amplitude of the discharges</p> <p><i>Anacyclus pyrethrum</i> has a dose dependent protective effect, increase the latency and threshold and decrease the duration of extensions.</p> <p><i>Laurus nobilis</i> is protective against tonic convulsions</p> <p><i>Origanum majorana</i> has an effect on duration and latency</p> <p><i>Nigella sativa</i> has a protective effect and an effect on duration, latency on PTZ and Picrotoxicine models. On MES models, there is no effect on latency and duration</p> <p><i>Piper longum</i> has a protective effect, decrease the mortality and increase the latency on PTZ and pilocarpine models. Not on STN and 4-aminopyridine models.</p> <p><i>Ferula gummosa</i> has a protective dose-dependent effect</p> <p><i>Ferula assa-foetida</i> and <i>Brassica nigra</i> decreases the intensity and duration</p> <p><i>Caesalpinia bonduc</i> has a protective effect on seizures</p> <p><i>Lavandula stoechas</i> increases the latency, decrease the mortality and severity of seizures</p> <p><i>Ruta graveolens</i> increases latency of tonic and myoclonic seizures</p>	Abdollahi et al., 2013
<i>Pimpinella anisum</i> L.	Compositae		Seeds	200										
<i>Anacyclus pyrethrum</i> (L.) Lag.	Apiceae		Roots	200, 400, 600										
<i>Laurus nobilis</i> L.	Lauraceae		Seeds	-										
<i>Origanum majorana</i> L.	Lamiaceae		Aerial parts	250, 500										
<i>Nigella sativa</i> L.	Renonculaceae		Seeds	250 and 500										
<i>Piper longum</i> L.	Piperaceae		Fruit	250 and 500										
<i>Ferula gummosa</i> Boiss.	Apiaceae		Resin	40 et 80										
<i>Ferula assa-foetida</i> L.	Apiaceae		Resin	2,5, 5, 10, 20, 250, 500 -										
<i>Brassica nigra</i> (L.) K.Koch	Brassicaceae		Fruit	-300, 500, 750										
<i>Caesalpinia bonduc</i> (L.) Roxb.	Cesalpinaceae		Fruit	600, 800										
<i>Lavandula stoechas</i> L.	Lamiaceae		Aerial parts	600										
<i>Ruta graveolens</i> L.	Rutaceae		Aerial parts	100, 300, 500, 800, 1000										

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

Spring	e													
<i>Syzygium aromaticum</i> (L.) Merr. & L.M.Perry	Myrtaceae	Iran	-	-	<i>In vivo</i>	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	Countries	Part of specie	Preparation way	Type of models	Name of models	Extracts	Administration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference
<i>Baccharis serraefolia</i> DC.	Compositae	Mexico	Leaves	-	<i>In vivo</i>	PTZ, STN	Methanolic	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
<i>Millettia thonningii</i> (Schum. & Thonn.) Baker	Leguminosae	Cameroun	Seeds	Decoction, infusion	<i>In vivo</i>	MES, NMDA, PTZ, INH, picrotoxine, STN	Methanolic	IP et PO	100, 200, 500, 1000 mg/kg	Diazepam, clonazepam	Percentage of protection against seizures and latency of convulsions	-	<i>Millettia thonningii</i> : 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) <i>Ocimum tenuiflorum</i> : Protective effect on MES, picrotoxine (complex interaction with NMDA receptor), PTZ, STN (glycine receptors involved) <i>Securidaca longepedunculata</i> : Protective effect on PTZ, MES, INH, Picrotoxine, STN	Okomolo et al., 2011
<i>Ocimum tenuiflorum</i> L.	Polygalaceae		Bark of roots	Decoction			Ethanollic							
<i>Securidaca longepedunculata</i> Fresen.	Polygalaceae		Roots	-			Aqueous							

Species	Family	Countries	Part of specie	Preparation way	Type of models	Name of models	Extracts	Administration	Dose	Gold standard	Observed criteria	Toxicity	Results	Reference
<i>Zapoteca portoricensis</i> (Jacq.) H.M.Hern.	Mimosaceae	Nigeria	Roots	-	<i>In vivo</i>	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. <i>Zapoteca portoricensis</i> Therapeutic index (Ti) = 2.1 LD 50 : 587,14 mg/kg <i>Cleome rutidosperma</i> Ti = 1.7 - LD 50 : 102 mg/kg <i>Cynodon dactylon</i> Ti = 1.6 - LD 50 : 708 mg/kg <i>Holarrhena floribunda</i> Ti = 2.9 - LD 50 : 200 mg/kg <i>Newbouldia laevis</i> Ti = 3.3 - LD 50 : 550 mg/kg <i>Tetrapleura tetraptera</i> Ti = 4.0 - LD 50 : 165 mg/kg	Akah et al., 1997
<i>Cleome rutidosperma</i> DC.	Capparidaceae		Roots											
<i>Cynodon dactylon</i> (L.) Pers.	Poaceae		Leaves											
<i>Holarrhena floribunda</i> (G.Don) T.Durand & Schin	Apocynaceae		Leaves											
<i>Newbouldia laevis</i> (P.Beauv.) Seem.	Bignoniaceae		Leaves											
<i>Tetrapleura tetraptera</i> (Schum. & Thonn.) Taub.	Leguminosae	Fruit												
<i>Cyperus articulatus</i> L.	Cyperaceae	Cameroon	Rhizome	Decoction	<i>In vitro</i>	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	Countries	Part of specie	Preparation way	Type of models	Name of models	Extracts	Administration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference
<i>Rubus brasiliensis</i> Mart.	Rosaceae	Brazil	Leaves	-	<i>In vivo</i>	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
<i>Euphorbia tirucalli</i> L.	Euphorbiaceae	Somalia	Aerial parts	-	<i>In vivo</i>	PTZ	Ethanollic	IP	250 mg/kg	-	Percentage of protection against seizures	Maximum tolerated dose in mice: 500 mg/kg	Protective effect	Samuelsson et al., 1992
<i>Jatropha curcas</i> L.	Euphorbiaceae		Roots	PTZ et STN										
<i>Cymbopogon citratus</i> (DC.) Stapf	Poaceae	Brazil	Leaves	Infusion	<i>In vivo</i>	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
<i>Gardenia resinifera</i> Roth	Rubiaceae	India	Resin	Oil	<i>In vivo</i>	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	Countries	Part of specie	Preparation way	Type of models	Name of models	Extracts	Administration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference
<i>Uncaria rhynchophylla</i> (Miq.) Miq. ex Havil	Rubiaceae	Taiwan	-	-	<i>In vitro</i> & <i>in vivo</i>	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
<i>Qualea grandiflora</i> Mart.	Vochysiaceae	Brazil	Leaves	-	<i>In vivo</i>	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	Countries	Part of specie	Preparation way	Type of models	Name of models	Extract	Administration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference
<i>Rhoicissus tridentata</i> (L.f.) Wild & R.B.Drumm	Anacardiaceae	South Africa	Leaves	-	<i>In vitro</i> & <i>in vivo</i>	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	Ethanol ic	-	0,001, 0,01, 0,1, 1, 10 mg/ml	-	Percentage of binding to receptor GABA A and protection against seizures	-	<i>Rhoicissus tridentata</i> : Binding at 96 % <i>Rhus rehmananniana</i> : Binding at 96 % <i>Hoslundia opposita</i> : Binding at 95 % and 60 % of protection against seizures <i>Clausena anisate</i> : Binding at 91 % <i>Leonotis leonurus</i> : 110 % of protection against seizures on PTZ, picrotoxine, NMDA and not bicuculline <i>Leonotis leonurus</i> : Binding at 107 %	Risa et al., 2004
<i>Rhus rehmananniana</i> Engl.	Anacardiaceae		Leaves	Ethanol ic										
<i>Hoslundia opposita</i> Vahl	Lamiaceae		Leaves	Ethanol ic										
<i>Clausena anisata</i> (Willd.) Hook.f. ex Benth.	Rutaceae		Roots	Ethanol ic										
<i>Leonotis leonurus</i> (L.) R.Br.	Lamiaceae		Roots	Aqueous and ethanol ic										
<i>Leonotis leonurus</i> (L.) R.Br.	Lamiaceae		Bulb	Ethanol ic										
<i>Dorstenia arifolia</i> Lam.	Moraceae	Brazil	Rhizome	-	<i>In vivo</i>	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
<i>Spondias mombin</i> L.	Anacardiaceae	Nigeria	Leaves	-	<i>In vivo</i>	STN, picrotoxine	Ethanol ic, methanolic, aqueous	IP	25, 50, 100 mg/kg	Phenobarbital	Percentage of protection against seizures	LD 50 methanolic: 1,1 g/kg et ethanol ic: 480 mg/kg	Protective effect on picrotoxine model for ethanol ic extract, no effect on STN model and no effect of the aqueous extract	Ayoka et al., 2006

Species	Family	Countries	Part of specie	Preparation way	Type of models	Name of models	Extracts	Administration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference
<i>Searsia dentata</i> (Thunb.) F.A.Barkley	Anacardiaceae	South Africa	Leaves	-	<i>In vitro</i>	Antagonist effect on NMDA receptors	Ethanollic	-	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
<i>Searsia pyroides</i> (Burch.) Moffett	Anacardiaceae													
<i>Gladiolus dalenii</i> Van Geel	Iridaceae	Cameroon	-	Maceration	<i>In vitro & in vivo</i>	GABA concentration in the brain, PTZ, MES	Lyophilized and aqueous extract	PO	150, 1000 mg/kg	Clonazepam, diazepam	Concentration measure of intracerebral 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
<i>Mitragyna africana</i> (Willd.) Korth.	Rubiaceae	Nigeria	Bark of stem	-	<i>In vivo</i>	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	Countries	Part of specie	Preparation way	Type of models	Name of models	Extracts	Administration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference
<i>Searsia dentate</i> (Thunb.) F.A.Barkley	Anacardiaceae	South Africa	Leaves	-	<i>In vitro</i>	Binding to NMDA and AMPA receptors	Ethanollic	-	-	-	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
<i>Searsia pyroides</i> (Burch.) Moffett	Anacardiaceae													
<i>Acanthus montanus</i> (Nees) T.Anderson	Acanthaceae	Cameroon	Leaves	Decoction	<i>In vivo</i>	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	-	<i>Acanthus montanus</i> : Protective effect on all models except for NMDA <i>Alchornea laxiflora</i> : Protective effect on NMDA (100%) and STN (75%) <i>Hyptis spicigera</i> : Protective effect on PTZ (87.5%) and STN (100%) <i>Microglossa pyrifolia</i> : High protective effect on all models, more moderated on STN (50%) <i>Bauhinia reticulata</i> : Protective effect on NMDA (100%), PTZ (32.5%), STN (75%) <i>Voacanga africana</i> : Protective effect on all models except for PIC	Bum et al., 2009
<i>Alchornea laxiflora</i> (Benth.) Pax & K.Hoffm.	Euphorbiaceae													
<i>Hyptis spicigera</i> Lam.	Lamiaceae													
<i>Microglossa pyrifolia</i> (Lam.) Kuntze	Compositae													
<i>Bauhinia reticulata</i> DC.	Cesalpiniaceae													
<i>Voacanga africana</i> Stapf ex Scott-Elliot	Apocynaceae													
<i>Lannea barteri</i> (Oliv.) Engl.	Anacardiaceae													

Species	Family	Countries	Part of specie	Preparation way	Type of models	Name of models	Extracts	Administration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference
<i>Carissa spinarum</i> L.	Apocynaceae	Nigeria	Roots	-	<i>In vivo</i>	PTZ, Pilocarpine, NMDA, aminophylline, INH, STN, HEK embryonal cells	Ethanollic	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
<i>Solanum torvum</i> Sw.	Solanaceae	Philippines	Aerial parts	Aqueous decoction	<i>In vivo</i>	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	Countries	Part of specie	Preparation way	Type of models	Name of models	Extracts	Administration	Doses	Gold standard	Observed criteria	Toxicity	Results	Reference
<i>Ficus platyphylla</i> Delile	Moraceae	Nigeria	Bark	-	<i>In vivo</i>	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 dependent / 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
<i>Telfairia occidentalis</i> Hook.f.	Cucurbitaceae	Nigeria	Leaves	-	<i>In vivo</i>	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
<i>Latin America</i>			
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
<i>Asia</i>			
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
<i>Africa</i>			
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	-	-