Seizure 2000; **9**: 96–107
doi: 10.1053/seiz.1999.0378, available online at http://www.idealibrary.com on IDEAL

Review on phytotherapy in epilepsy

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Key words: antiepileptic; anticonvulsant; epilepsy; plant; herbal medicine.

INTRODUCTION

The epilepsies are among the most common of neurological disorders, prevalence is about 1%[1]; based on this figure, there are 500 000 people in the UK who suffer from epilepsy. Approximately 70% of patients with epilepsy are well controlled by monotherapy with currently available antiepileptic drugs[2]. Another 5–10% of patients are stabilized by the addition of another antiepileptic drug but there remains over 20% of patients whose seizures are not controlled[2]. By estimation, in the UK alone, 100 000 patients with epilepsy require more effective antiepileptic drug treatments. The last 10 years have been an exciting time for both patients with epilepsy and the health profession. Five new antiepileptic drugs, gabapentin, lamotrigine, tiagabine, topiramate and vigabatrin, have been marketed in the UK and other countries. They have all been shown to be effective in short-term add-on clinical trials in patients with uncontrolled epilepsy. However, in long-term study, Wong showed that less than a quarter of patients with severe epilepsy will still be taking the new antiepileptic drugs (gabapentin, lamotrigine and vigabatrin) after six years, few patients will be seizure free[3]. He concluded that the task to improve the prognosis of severe epilepsy has not been accomplished. Therefore, phytomedicines can potentially play an important role in the development of new antiepileptic drugs.

Many plants were known for their anticonvulsant activity. Various phytochemical and pharmacological studies have been carried out on these anticonvulsant plants. In fact, a review article[4] was previously published with regards to plants with anticonvulsant activity. Thus, the aim of this article is to give an up-to-date literature review on plants/natural products which have been used traditionally for the treatment of epilepsy or those which have been shown to possess anticonvulsant activity.

MATERIALS AND METHOD

An extensive literature search was carried out in 1999 using the Science Citation Index of BIDS (Bath Information Data Services), 1981 to date and PubMed (Medline), 1966 to date. The keywords used in the search were: Epilepsy, Plant, Anticonvulsant, Natural product, Antiepileptic, Herbal, Seizure, Traditional, Remedies. From the literature search, all plants/herbal preparations that are used ethnomedically to treat epilepsy or those which have been tested for anticonvulsant activity are included in this review.

RESULTS

Over 50 references were found in which plants or herbal preparations have been tested for their anticonvulsant activity in *in vivo/in vitro* studies (see Table 1) or clinical studies (see Table 2).

DISCUSSION

Models for testing antiepileptic drugs

Seizures can be induced in animals by a wide range of experimental methods such as electrical or chemical stimulation. The choice of a particular model depends

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Table 1: *In vivo/in vitro* studies on antiepileptic plants.

This table comprises an extensive list of plants (arranged in alphabetical order) used ethnomedically to treat epilepsy/convulsion or in some way tested for therapeutic activity against epilepsy. The following explains the abbreviations used in the table.

Plants:- The scientific names (in Latin binomials) of the plants are given as they appear in the references. The family in which the plants belong to are given in brackets.

HP:- Herbal preparations. In some studies, instead of testing on one single plant, the effects of herbal preparations (which consist of several plants) were investigated.

ETH:- Ethnic origin. The name of the countries in which the plant is used traditionally to treat epilepsy is given.

PT:- Part of the plant tested.

Abbreviations: ap, aerial parts; bk, bark; bl, bulb; fl, flower; fr, fruit; j, juice; lf, leaf; pl, peel; rb, root bark; rt, root; rz, rhizome; sb, stem bark; sd, seed; sh, shallot; sho, shoots; st, stem; stk, stalk; tb, tuber; wd, wood; wp, whole plant (roots, stems, leaves and flowers).

ROA:- Route of administration.

Abbreviations: ip, intraperitoneal; iv, intravenous; po, per os (orally); sc, subcutaneous.

Activity:- Anticonvulsant/Anti-epileptic activity

Keys: $+$: active; $-$: inactive; $\uparrow$: increase/stimulate; $\downarrow$: decrease/inhibit; ACV, anticonvulsant effect; AEP, Anti-epileptic effect; AIC, acetylcholine-induced convulsions; AUIS, audiogenic-induced seizures; ChIC, chemo-induced convulsions; CMIC, champhor-induced convulsions; CZIC, corazole-induced convulsions; DIA, dependent inhibiting action; EEG, electroencephalogram, EIC, electrically-induced convulsions; GABA, γ-aminobutyric acid; HIC, histamine-induced convulsions; KAIC, kainic acid-induced convulsions; LIS, leptazole-induced seizure; MES, maximum electroshock seizures; MIS, metrazole-induced seizures; 3-MCAIC, 3-mercaptopropionic acid-induced convulsions; NMDLAIC, N-Methyl-DL-aspartate-induced convulsions; NMDAMN, N-Methyl-D-aspartate acid-mediated neurotransmission; PIC, picrotoxin-induced convulsions; PLIC, pilocarpine-induced convulsions; PTZ, pentylenetetrazole; PZIC, pentylenetetrazole-induced convulsions; SIS, strychnine-induced seizures; TCES, transcorneal electroshock.

ACWSD:- Activity compared with synthetic drugs. A comparison in the potency of activity with synthetic drugs currently used in the market.

Keys: $>$: more than; $<$: less than; $=$: equal to; ADE, antidiarrhoeic effect; BND, benzodiazepine; DPR, desipramine; DZ, diazepam; LOP, loperamide; PB, phenobarbitone; PHT, phenytoin; TMP, trimipramine; VA, valeproic acid.

TM:- Testing models. *vv: in vivo*; *vt: in vitro*.

Animals species used: am, albino mice; ar, albino rats; gp: guinea pigs; mk: monkeys; m: mice; r: rat; sm: swiss mice; wch: white chicks; wm: wister mice; wr: wister rats

apls, anterior part of left side; b, brain; cc, cortical cortex; cw, cortical wedges; hs, hippocampal slices; igp, ileum of guinea pigs; sc, spinal cortex; tram, toad rectus abdomen muscular; ts, tactile stimulation.

AE/C (Active extracts/constituents):- Plants extracts or constituents that have been tested for anticonvulsant activity.

Keys: AE, alcoholic extract; AEO, aromatic essential oil; Alk, alkaloid; Alk E, alkaloidal extract; Aq E, aqueous extract; ASFA, aqueous solution of mixed fatty acids; BE, boiled extract; 6-BZH, 6-Benzoylheteratisine; 1-BZN, 1-benzoylnapelline; ChE, chloroform extract; E, extract; EE, ethanolic extract; EO, essential oil; HC, hydroalcoholic extract; IP, imperatarin; LAE, lyophilised aqueous extract; ME, methanolic extract; NEO, neutral essential oil; SDE, steam distillate extract; SP, scoparone; WE, water extract; VDA, vacuum dried aqueous extract; Xn, xanthoxyletin.

SE/Tox:- Possible side effects or toxicity data reported.

Keys: AX, ataxia; BC, behavioural changes; CNSD, central nervous system depressant; CNSS, central nervous system sedative; D, depression; HA, hypnotic action; HG, hypoglycaemic; HP, hypothermic; HPT, hypotension; PB, phenobarbitone; RMA, reduced motor activity; S, sedative; TE, transient excitation; TS, transient stimulation.

REM (Remarks):- Other activities reported.

Keys: A, analgesic; AB, antibacterial; AC, anticancer; AD, antidepressant; ADE, antidiarrhoeic effect; AHT, antihypertensive; AI, anti-inflammatory; AM, antimalarial; AMG, antimigraine; AN, anthelmintic; ANX, anxiolytic; AP, antipyretic; AR, antiarrhythmic; B, bactericidal; CBRL, central benzodiazepine receptor ligand; F, fungicidal; HNC, hypnotic; HYM, hypomotility; IE, initial excitation; IT, intestinal transient; MR, muscle relaxant; NAX, no ataxia; NBA, neuromuscular blocking agent; NCNSD, no CNS depressant; NMR, no muscle relaxant; NRP, neuroleptic; PTS, ptosis; TQ, tranquillizing

RN:- References as in the reference section.

Plants	HP	ETH	PT	ROA	Activity	ACWSD	TM	AE/C	SE/Tox	REM	RN
Abrus precatorius L. (Leguminosae)	—	India	rt	—	+ LIS − SIS	—	—	—	S CNSD	—	5
Aconitum species (Ranunculaceae)	—	China	—	iv	DIA/central neurons	= DZ	*vt*/hs	1-BZN, 6-BZH	—	—	6 7
Acorus calamus (Araceae)	—	—	—	—	+ MIS	—	—	AEO,NEO	—	—	4
Adonis vernalis (Ranunculaceae)	—	—	—	—	+ ACV	—	—	—	—	—	4
Afraegle paniculate (Rutaceae)	—	Nigeria	st,rt	ip	+ LIS, + ACV	—	*vv*/m	ME	S CNSD	A,AP	4, 5
Albizia lebbek Benth. (Leguminosae)	—	India	rt,lf	ip	++ PIC, PZIC + MIS, ↑ GABA level in the brain	—	*vt*/b *vv*/am	Chloroform fraction of ME	—	—	5 8
Albizia zygia Macribide (Leguminosae)	—	Africa	lf	po	− LIS − SIS	—	—	—	—	—	5
Allium ascalonicum (Liliaceae)	—	—	sh	—	+ LIS	—	—	AE	HPN	A	5
Allium cepa L. (onion) (Liliaceae)	—	—	bl	—	+ LIS − SIS	—	—	AE	HPN	A,B	5
Allium sativum L. (garlic) (Liliaceae)	—	—	bl	—	+ LIS	—	—	AE	HG,HPT S	AB,B AN,F	5
Alstonia boonei D.Wild (Apocynaceae)	—	Nigeria	sb	—	+ LIS	—	—	AE Echitamine	— S	CNSD	5
Alstonia schoaris R.Br. (Apocynaceae)	—	India	sb	—	—	—	—	Alk	HPT	AM,AC NBA	5
Annona muricata L. (Annonaceae)	—	—	fr	po	− LIS − SIS	—	—	—	—	—	5
Apium graveolens (Umbelliferae)	—	—	—	—	+ ACV	—	—	—	—	—	4
Areca catechu (Palmae)	—	—	—	iv sc	↓ uptake of GABA & β-alanine	—	*vt*/sc	Arecaidine Guvacine	—	—	9
Artemisia verlotorum (Asteraceae)	—	Brazil	wp	ip	+ MES, PZIC ↑ latencies on 3-MCAIC & PLIC	—	*vv*/m	Helietin	—	A	10
Asparagus officinalis (Liliaceae)	—	—	—	—	+ LIS	—	—	—	—	—	4
Astragalus centralpinus (Leguminosae)	—	—	—	—	+$BaCl_2$, AIC HIC	—	—	—	—	—	4
Atractylodes lancea (Asteraceae)	—	China	—	ip	+ MIS − PZIC, PIC	= PHT Additive action with PHT at subeffective doses	*vt*/hs *vv*/wr	β-eudesmol	—	—	11
Baccharis serraefolia (Asteraceae)	—	Mexico	lf	po ip	Significantly delayed the onset of tonic seizures induced by strychnine & pentylenetetrazole	ADE = LOP	*vv*/m *vt*/igp	—	—	ADE	12
Basslla alba L. (Basellaceae)	—	India	lf,st	—	− LIS − SIS	—	—	AE	S,CNSD	—	5
Basslla ruba L. (Basellaceae)	—	India	lf,st	—	− LIS − SIS	—	—	AE	S,CNSD	—	5
—	Brahmighritham, an Ayurvedic herbal formula:			po	+ PZIC	= BND	*vv*/ar	—	—	—	13
	Herpestis monniera L. (Scrophulariaceae)	India	lf,st								
	Cyperus rotundus L. (Cyperaceae)	India & Cylon	tb								
	Saussurea lappa Clarke (Asteraceae)	Himalaya & Kashmir	tb								
	Ghee (dehydrated form of butter)										
—	Brahmi Rasayan, an Ayurvedic herbal formula:	—		po	+ EIC, + ChlC	—	*vv*/m, r	—	S, ↑ HA of PB	AC	14
	Herpestis monniera L. (Scrophulariaceae)		lf								
	Eugenia caryophyllata Thunb. (Myrtaceae)		fl								
	Piper longum L. (Piperaceae)		stk								
	Elettaria cardamomum Maton (Zingiberaceae)		sd								
Caesalpinia bonduc (Leguminosae)	—	—	rt,sd	—	+ LIS, + SIS	—	—	—	—	—	5

Plants	HP	ETH	PT	ROA	Activity	ACWSD	TM	AE/C	SE/Tox	REM	RN
Calliandra portoricensis (Leguminosae)	—	Africa, Nigeria	rt,st	ip	++ LIS, ++ SIS, + MIS	—	—	AqE, Alk E	S	A	5 15
Cannabis sativa (Cannabinaceae)	—	—	—	—	+ ACV	—	—	Cannabinoid	—	—	4
Canscora decussata (Gentianaceae)	—	—	wp	po	+ ACV	<PHT	*vv*/ar	AE ChE	—	—	16 4
Capparis baduca (Capparaceae)	—	—	—	—	+ ACV	—	—	Alk	—	AI	4
Capsicum annum L. (Solanaceae)	—	—	fr	—	− LIS − SIS	—	—	—	—	—	4
Carica papaya L. (Caricaceae)	—	—	rt	—	+ LIS + SIS	—	—	E	—	—	5
Casimiroa edulis (Rutaceae)	—	Mexico	lf	po sc	+ MIS	=PHT, PB	*vv*/wr	VDA	—	—	17
Centella asiatica L. (Umbelliferae)	—	—	—	—	− LIS − SIS	—	—	AE Alk	S	—	5
Cerbera odollam (Apocynaceae)	—	Vietnam, Cambodia	lf	ip	+ PZIC	—	*vv*/m	—	Potentiated PB hypnotic effect	A	18
Cinchona officinalis (Rubiaceae)	—	—	—	—	+ ACV	—	—	Quinine	—	—	4
Cissampelos pareira L. (Menispermaceae)	—	—	rt	—	+ LIS + SIS	—	—	Alk	CNSD, S	—	5
Citrus aurantifolia (Rutaceae)	—	—	fr	—	− LIS − SIS	—	—	Citral (lime)	CNSD	—	5
Citrus aurantium L. (Rutaceae)	—	—	pl	—	++ LIS + SIS	—	—	EO	CNSD	—	5
Clausena anisata (Rutaceae)	—	Nigeria	rt,sb	ip	+ LIS	—	—	AE, ME ChE: SP, IP, Xn, HC	CNSD, S	A,AP	4, 19
Cleome cileata (Capparidaceae)	—	Nigeria	lf	ip	++ MIS + PZIC	—	*vv*/am	Aq E	CNSD	—	20
Cnestis glabra (Connaraceae)	—	—	—	—	+ ACV	—	—	Glabrin	—	—	4
Cola acuminata L. (Sterculiaceae)	—	—	sb,fr	—	− LIS − SIS	—	—	—	TS followed by D	—	5
Convolvulus arvensis (Convolvulaceae)	—	—	—	—	+ ACV	—	—	—	—	—	4
—	Cow's urine concoction	Nigeria		ip	− ACV	—	*vv*/am	ChE	Reduce tone of smooth muscles, HPT, CNSD, HP, HG, loss of vasoconstr-uctor tone, cardiac depression and cardiac arrest.	—	21
	Nicotiana tabacum (Solanaceae)		lf								
	Ocimum viride (Lamiaceae)		lf								
	Citrus limon (Rutaceae)		j								
	Allium sativum (Liliaceae)		lf								
	Allium cepa & *Allium ascarbicum* (Liliaceae)		bl								
	Trona Cow's urine (Bosndama)										
Cucurbita pepo L. (Cucurbitaceae)	—	—	—	—	− LIS − SIS	—	—	—	—	—	5
Cymbopogon citratus (Gramineae)	—	Brazil	lf	po ip	− ACV	—	*vv*/m, r	EO	HP	↓ IT	22
Cynodon dactylon L. (Gramineae)	—	Nigeria	lf	ip	+ PZIC, MIS	—	*vv*/am	Aq E	CNSD, AX	—	5, 20
Cyperus articulatus (Cyperaceae)	—	Africa, L.America	rz	po	Inhibited spontaneous epileptiform discharge ↓NMDAMN	—	*vv*/m, r *vt*/cw	WE	—	—	23
Cyperus rotundus L. (Cyperaceae)	—	—	rt	—	+ LIS, SIS	—	—	AE	—	—	5
Delphinium consolida (Ranunculaceae)	—	—	—	—	+ ACV	—	—		—	—	4
Desmodium adscendens (Leguminosae)	—	Africa	lf	ip	+ PZIC, KAIC − MIS	—	*vv*/ sm, wr	EE	HP	A	24
Duboisia leichhardtii (Solanaceae)	—	—	—	—	+ ACV	—	—	—	—	—	4
Echinacea purpurea (Asteraceae)	—	—	—	—	+ ACV	—	—	—	—	—	4
Echium vulgare (Boraginaceae)	—	—	—	—	+ ACV	—	—	E	—	—	4
Egletes viscosa L. (Asteraceae)	—	Brazil	fl	po	+ PZIC	—	*vv*/m	EO	—	A, AB (S.aureus)	25
Elaeocarpus ganitus Roxb. (Elaeocarpaceae)	—	—	sd	po	+ MES, − MIS	—	*vv*/*a*m	EE ASFA	—	—	26

Plants	HP	ETH	PT	ROA	Activity	ACWSD	TM	AE/C	SE/Tox	REM	RN
Eryngium feotidum L. (Umbelliferae)	—	Jamaica, Caribbean, S.America	lf,st	ip	+ PIC	=PB	*vv*/r	Aq E BE SDE	—	—	27
Erythroxylum spp. (Erythroxylaceae)	—	—	—	—	+ MIS	—	—	Cocaine	—	—	4
Euphorbia hirta L. (Euphorbiaceae)	—	—	wp	ip	− ACV	—	*vv*/m, r	LAE	S	A, AD	28
Euphorbia pilulifera (Euphorbiaceae)	—	—	—	—	Monotoxic and prophylactic action against lethal egg-white shock in guinea pigs	—	*vv*/*gp*	—	—	—	4
Galicia spp. (Galiaceae)	—	—	—	—	+ ACV	—	—	—	—	—	4
Galium cruciata (Rubiaceae)	—	—	—	—	Folk medicine	—	—	—	—	—	4
Galium sylvaticum (Rubiaceae)	—	—	—	—	Folk medicine	—	—	—	—	—	4
Galphimia glauca (Malpighiaceae)	—	Mexico	ap	ip	− ACV	—	*vv*/am	ME: Galphimine B	S, CNSD	—	29
Gastrodia elata (Orchidaceae)	—	—	—	—	+ ACV	—	—	—	—	—	4
Ginkgo biloba (Ginkgoaceae)	—	Africa	—	po	↓ ECS induced diacyl-glycerols and fatty acids accumulation; selective sites of drug action in CNS	—	*vv*/wr cc,hs	E	—	—	30
Haplophyllum perforatum (Rutaceae)	—	—	sd	—	+ CZIC, CMIC	—	—	—	—	—	4
Haplophyllum lociosum (Rutaceae)	—	—	—	—	+ LIS, CZIC	—	—	—	—	—	4
Haplophyllum spp. (Rutaceae)	—	—	—	—	+ ACV	—	—	—	—	—	4
Heracleum sibiricum (Umbelliferae)	—	—	—	—	+ EIS, PZIC, CZIC − SIS	—	—	—	—	—	4
Heracleum verticillatum (Umbelliferae)	—	—	—	—	+ MES, PZIC, CZIC − SIS	—	—	—	—	—	4
Herpestris monniera (Scrophulariaceae)	—	—	—	—	—	—	—	—	—	TQ	4
Holarrhena floribunda (Apocynaceae)	—	Nigeria	lf	ip	+ PZIC, MIS	—	*vv*/am	Aq E	CNSD, AX	—	20
Hypericum calycinum L. (Hypericaceae)	—	Greece, Romania	wp	ip	—	= DPR, TMP	*vv*/m	E	—	AD	31
Hypericum perforatum L. (Hypericaceae)	—	Greece, Romania	wp	ip	—	= DPR, TMP	*vv*/m	E	—	AD	31
Ipomoea stans (Convolvulaceae)	—	Mexico	wd	iv	+ EIC, PZIC (after long-term treatment)	= VA	*vv*/am	—	—	—	32
Jatropha curcas L. (Euphorbiaceae)	—	—	rt	—	++ LIS, + SIS	—	—	—	—	—	5
Jatropha gossypiifolia L. (Euphorbiaceae)	—	—	rt, lf	—	+ LIS, SIS	—	—	—	S, CNSD	—	5
Kochia prostrata (Chenopodiaceae)	—	—	—	—	+ SIS	—	—	EE	—	—	4
Lanata camara L. (Verbenaceae)	—	—	rt,lf	iv	+ LIS, SIS	—	*vv*/m	EO AE	CNSD	F	5
Lanata microphylla (Verbenaceae)	—	Brazil	lf	—	+ LIS, SIS	—	*vv*/m	EO AE	CNSD	F	5
Leonurus cardiaca (Lamiaceae)	—	—	—	—	+ ACV	—	—	—	—	—	4
Liacaria puchurymajor (Lauraceae)	—	—	—	—	+ TCES	—	—	EO	RMA	—	4
Lonchocarpus sericeus (Leguminosae)	—	—	rt	—	− LIS, SIS	—	—	—	CNSD	—	5
Magnolia officinalis (Magnoliaceae)	—	China Japan	bk	ip	Prevent tonic extensor convulsions	—	*vv*/am wch, wr	Magnolol Honokiol	AX, S CNSD	HYM, PTS, MR	4, 33
Magnolia obovata (Magnoliaceae)	—	—	—	—	+ SIS, + PIC, + PZIC	—	—	—	—	AB	4
Marsilea rajasthanesis (Marsileaceae)	—	—	—	—	+ ACV, AEP	—	—	—	—	—	4
Marrubium vulgare (Lamiaceae)	—	—	lf, fl	—	—	—	—	—	—	AMG	4
Maprounea africana (Euphorbiaceae)	—	Congo	lf	ip	Delayed the onset of clonic convulsions induced by PTZ; − MIS, PIC, PLIC & KAIC	—	*vv*/sm wr	—	HP	↑ HA of PB	34
Matricaria recutica L. (German Chamomile) (Asteraceae)	—	Europe US	fl	iv	− PZIC	—	*vv*/m	Apigenin	S	CBRL, ANX	35

Plants	HP	ETH	PT	ROA	Activity	ACWSD	TM	AE/C	SE/Tox	REM	RN
Maytenus spp. (Celastraceae)	—	Brazil	lf	po, ip	− TCES, ChIC	—	*vv*/sm r	WE	CNSD (ip only)	HNC (ip only)	36
Melia azedarach L. (Meliaceae)	—	—	rb	—	++ SIS, LIS	—	—	—	S, CNSD	—	5
Momordica balsamina L. (Cucurbitaceae)	—	—	lf, fr	—	− LIS, SIS	—	—	—	CNSD	—	5
Momordica charantia L. (Cucurbitaceae)	—	—	sho, lf, fl	—	− LIS, SIS	—	—	—	CNSD	—	5
Moringa oleifera Juss. (Moringaceae)	—	—	rt	—	++ SIS, LIS	—	—	—	S, CNSD	—	5
Nardostachys jatamansi (Valerianaceae)	—	—	—	—	+ ACV	—	—	—	—	AR	4
Newboldia leavis (Bignoniaceae)	—	Nigeria	lf	ip	+ PZIC, MIS	—	*vv*/am	Aq E	CNSD, AX	—	20
Nicotiana tabacum L. (Solanaceae)	—	—	—	—	++ SIS, LIS	—	—	AE	S, CNSD	IE, A	5
Ocimum americanum L. (Lamiaceae)	—	—	lf	—	++ LIS	—	*vv*/m	—	S, CNSD	—	5
Ocimum basilicum L. (Lamiaceae)	—	—	lf	—	++ LIS	—	*vv*/m	—	S, CNSD	A	5
Ocimum gratissimum L. (Lamiaceae)	—	—	—	—	+ LIS − SIS	—	*vv*/m	AE	S, CNSD	A	5
Paeonia radix J.P. (Paeoniaceae)	—	Japan	rt	po	+ ACV; protective effect on neuron damage	—	*vt*/apls	WE, Gallo-tannin	—	—	37
Panax ginseng C.A. (Araliaceae)	—	China	lf, rt	ip	− MIS, PIC	—	—	—	—	NRP, A, AP	4, 38
Patrina intermedia (Valerianaceae)	—	—	—	—	+ SIS	—	—	—	—	—	4
Pausinystalia yohimbe (Rubiaceae)	—	—	bk	ip	+ ACV (antagonised by prior administration of clonidine or prazosine	—	*vv*/m; ts	Yohimbine (indole alkaloid)	—	—	39
Picnomon acarna (Asteraceae)	—	—	—	—	+ ACV	—	—	Alk	S	—	4
Piper guineense L. (Piperaceae)	—	Nigeria	fr	ip	+ AUIS, MIS & NMDLAIC, − PZIC	= PB	*vv*/m	WE, EE	—	NCNSD	40
Piper methyticum (Piperaceae)	—	—	—	—	+ SIS	—	—	—	—	—	4
Piper nigrum L. (Piperaceae)	—	China	fr	—	+ ACV (an antagonistic action at N-methyl-D-aspartic acid receptors)	—	*vv*/m *vt*/cw	WE	—	—	4, 41
Pithecellobium saman (Leguminosae)	—	—	—	—	+ PIC, AUIS	—	—	Alk	—	—	4
Plumbago zeylanica L. (Plumbaginaceae)	—	—	rt	—	+ LIS	—	—	—	S	A, AB	5
Portulaca oleracea L. (Portulacaceae)	—	—	wp	—	− LIS, SIS	—	—	—	—	—	5
Psidium guyanensis Pers (Myrtaceae)	—	Brazil	lf	po	+ PIC, SIS, PZIC & AIC	= PB (20 mg/kg)	*vv*/sm *vt*/tram	EO	—	—	42
Qingyangshen (root of *Cynanchum otophylum* Schnchid, of family Asclepiadaceae)	—	China	rt	ip	+ AEP, ↓ KAIC	—	*vv*/wr *vt*/b, hs	—	—	—	43, 44, 45, 46
Rauwolfia schueli (Apocynaceae)	—	—	—	—	—	—	—	—	—	—	5
Rauwolfia serpentina (Apocynaceae)	—	—	rt, sb	—	—	—	*vv*/mk	Reserpine	—	ANX AHT	4,5
Rauwolfia vomitoria Afz (Apocynaceae)	—	—	—	—	+ LIS, SIS	—	*vv*/m	Alk	S, CNSD & BC	A	5
Ricinus communis L. (Euphorbiaceae)	—	—	rt, sd	—	+ LIS − SIS	—	—	—	—	—	5
Roylea elegans (Lamiaceae)	—	—	—	ip	+ ACV	—	—	EE, WE	CNSD	—	4
Ruta chalepensis (Rutaceae)	—	Mexico USA, Africa, Asia	lf, st (ap)	ip	+ PZIC, EIC	—	*vv*/m *vt*/igp	ME, AE	↑ HA of PB	—	47
Salvia guaranitica St. Hill (Lamiaceae)	—	Latin America	ap	ip	− ACV	—	*vv*/m	Cirsiliol	S	HNC, − ANX, − MR	48

Plants	HP	ETH	PT	ROA	Activity	ACWSD	TM	AE/C	SE/Tox	REM	RN
Salvia nemorsa (Lamiaceae)	—	—	—	—	+ ACV	—	—	E	—	—	4
—	Saiko-keishi-to (SK) or TJ-960, a Japanese Kampo herbal medicine consisting of a mixture of 9 herbal drugs: *Paeonia radix* (Paeoniaceae) *Cinnamomum cortex* (Lauraceae) *Bupleurum radix* (Umbelliferae) *Zingiber rhizoma* (Zingiberaceae) *Glycyrrhiza radix* (Leguminosae) *Panax ginseng* (Araliaceae) *Scutellaria radix* (Lamiaceae) *Pinellia tuber* (Araceae) *Zizyphus fructus* (Rhamnaceae)	Japan	—	po	+ ACV; preventive effect against neuron damage; activates $GABA_A$ receptors; *Paeonia radix* showed statistically significant inhibition of PTZ induced EEG power spectrum changes	= PHT	*vv*/wr, r *vt*/hs, b	—	—	—	49, 50, 51, 52, 53
Solanum americana Jacq. (Solanaceae)	—	—	fr, lf	—	+ ACV, LIS	—	—	Scopoletin	CNSD, S	A	5
Solanum dasyphullum (Solanaceae)	—	—	—	—	—	—	—	—	—	—	4
Solanum gilo Raddi (Solanaceae)	—	—	fr	—	++ LIS, + SIS	—	—	—	—	—	5
Solanum indicum L. (Solanaceae)	—	—	fr	—	+ LIS − SIS	—	—	—	—	—	5
Solanum macrocarpon L. (Solanaceae)	—	—	fr, lf	—	− LIS, SIS	—	—	—	—	—	5
Solanum melongena L. (Solanaceae)	—	—	fr, lf	—	++ LIS, + SIS	—	—	Scopoletin Scoparone	—	—	5
Solanum nigrum L. (Solanaceae)	—	—	—	—	+ LIS & SIS	—	—	AE	TS followed by D & HPT	—	5
Solanum torvum Swartz (Solanaceae)	—	—	fr	—	+ LIS	—		—	TE followed by D	—	5
Spondias monbin L. (Anacardaceae)	—	—	fr	—	− LIS, SIS	—	—	—	—	—	5
Spondias monbin L. (Anacardaceae)	—	—	fr	—	− LIS, SIS	—	—	—	—	—	5
Talinum triangulare Wild (Portulacaceae)	—	—	wp	—	− LIS, SIS	—	—	—	—	—	5
Taraxacum spp. (Asteraceae)	—	—	—	—	+ ACV (weak)	—	—	—	—	—	4
Teclea simplifolia (Rutaceae)	—	—	—	—	+ ACV	—	—	—	—	—	4
Ternstroemia pringlei Rose (Theaceae)	—	Mexico	fl	ip	+ SIS	—	*vv*/am wr *vt*/igp	AE ME	—	—	47
Tetrapleura tetraptera (Mimosaceae)	—	Africa (west coast)	fr	ip	+ LIS	—	*vv*/am	VO	—	—	54
Thalictrum thumbergii (Ranunculaceae)	—	—	—	—	Antagonizes Phenamine Excitation	—	—	—	—	—	4
Thalictrum hernandezii (Ranunculaceae)	—	—	—	—	+ ACV	—	—	Hernandezine	—	—	4
Trema guineensis (Ulmaceae)	—	Gabon	lf	ip	+ PZIC − MIS, PIC & KAIC	—	*vv*/m	EE	HP	↑ HA of PB	55
Trema orientalis (Ulmaceae)	—	—	—	—	+ MIS	—	—	Flavonoidal mixture	CNSD	—	4
Uncaria sinensis (Rubiaceae)	—	—	—	—	+ ACV	—	—	—	—	—	4
Valeriana officinalis (Valerianaceae)	—	—	—	—	—	—	—	—	CNSS	AR	4
Veratrum viride (Liliaceae)	—	—	—	—	+ ACV	—	—	Veratrone-$MgSO_4$	—	—	4
Vinca erecta (Apocynaceae)	—	—	—	—	+ ACV		—	Ervinine	—	—	4
Xylopia spp. including: *X. aethiopica* A. Rich *X. carminativa* Fries *X. frustescens* Aubl. *X. grandiflora* St. Hil. *X. seriacea* St. Hil. (Annonaceae)	—	Brazil	—	—	− LIS & SIS	—	—	—	—	—	5
Zea mays L. (Gramineae)	—	—	—	—	–LIS, SIS	—	—	—	CNSD, S	—	5

Table 2: Clinical efficacy of four Chinese herbal treatments for epilepsy.

Treatment		Efficacy				
	No.	Markedly effective	Effective	Poorly effective	Ineffective	Aggravated
1	100	72%	12%	10%	6%	0%
Control	40	72.5%	20%	5%	2.5%	0%
2	32	66%	25%	9%		0%
3A or 3B	239	65.7	29.7	1.7%	2.9%	0%

Treatment 1. From Chen *et al.*[56]: Tablet: Semen Persicae 30 g, Radix Paeoniae Rubra 15 g, Flos Carthami 15 g, Rhizoma Ligustici Chuanxiong 15 g, Rhizoma Pinelliae 10 g, Rhizoma Cyperi 15 g, Medulla Tetrapanacis 8 g, Fructus Perillae 10 g, Pericarpium Citri Reticulatae Viride 15 g, Radix Glycyrrhizae 10 g, Pericarpium Citri Reticulatae 15 g, Pericarpium Arecae 10 g, and Cortex Mori Radicis 15 g.

Dose: 1/2 tablet per kg body weight three times a day.

Control: Patients were treated with conventional western medicines but were not specified by the authors.

Treatment 2. From Kuang *et al.*[57]: 'Qingyangshen' decoction: Root of *Cynanchum otophyllum* 10–30 g daily in two divided doses.

Treatment 3. From Wang[58]: Zhenxianling

A) Oral tablet: peach flower buds, yellow-flower patrinia, Rhizoma Valerianae, Radix Salviae Militorrhizae, concentrated powder of ox horn, pearl powder, Antelope's horn powder, earth-worm, human placenta and Borneolum. The extract of the above components was concentrated, dried and made into tablets of 0.45 g each.

Dose: 1–3 tablets twice a day.

B) Plaster: peach flower buds, yellow Daphne genkwa, Arisaema cum Bile, white dead silkworm, Radix Salviae Militorrhizae, Semen Strychni, Semen Hyoscyami and *Cynanchum otophyllum* Scnneid, which were mixed with sesame oil and boiled down by the slow fire. After the residuals infiltrated, the oil was set again on the fire and boiled down into syrup-like material which was then mixed with the yellow lead and finally put on a piece of kraft paper to make the adhesive plaster.

Dose: The plaster was placed on acupoint Shenque (Ren 8 exactly at the centre of the umbilicus), and changed every 3 days.

Markedly effective: Number of attacks reduced by $\geq$ 75%

Effective: Number of attacks reduced by $\geq$ 50% and $<$ 75%

Poorly effective: Number of attacks reduced by $\geq$ 25% and $<$ 50%

Ineffective: Number of attacks reduced by $<$ 25%

Aggravated: Number of attacks increased.

critically on the nature of the study, the questions posed, and hence the kinds of samples, recordings or observations required. However, for the drug screening, the models have to be simple and cheap to administer. It is out of the scope of this article to fully discuss every available method, excellence reviews have been conducted by Fisher (1989)[59], Jefferys (1994)[60] and Meldrum (1997)[61]. In this review we will only briefly mention the most common methods for evaluating the antiepileptic drugs in preclinical studies.

In vivo studies. Various chemicals have been shown to induce seizure in animals, different amount and different location of application will induce different type of seizures. Practically, any stimuli which are sufficiently strong to trigger off epileptic discharge in animal brain will trigger off seizures, thus, readers should not be too surprised to see so many methods to induce seizure in animal models. Table 3 is a summary of the most commonly used methods.

In vitro studies. *In vitro* studies now have a central role in fundamental studies of the epilepsies because they can help to unravel cellular mechanisms. The basic principle of the *in vitro* methods is to target on the mechanisms of seizure generation and propagation mentioned in the previous sections. Brain slices, tissue culture or neurones can be used for the study of antiepileptic effects of different drugs.

The most popular techniques used in *in vitro* studies are:

(1) Multichannel intracellular recordings to study local circuit.

(2) Voltage clamp to study membrane currents.

(3) Patch clamp to study individual channel, e.g. sodium channel.

(4) Binding to the neurotransmitters receptors and the enzyme involved in transmitters metabolism, e.g. GABA receptors and/or GABA transaminase binding.

Table 3: Common methods used to induce seizures in animal models.

(1) Models for acute simple partial seizures:

(A) Topical convulsants
(i) penicillin
(ii) bicuculline
(iii) picrotoxin
(iv) strychnine
(v) cholinergics
(vi) anticholinergics

(B) Acute electrical stimulation of cortical tissue
(C) GABA withdrawal

(2) Models for chronic simple partial seizures:
(A) Cortically implanted metal
(B) Crytogenic injury
(C) Ganglioside antibody injection

(3) Models for complex partial seizure:
(A) Kainic acid
(B) Tetanus toxin
(C) Injections into area tempesta
(D) Kindling model

(4) Models for generalized tonic–clonic seizures:
(A) Genetic
(i) Photosensitive baboons
(ii) Audigenic seizure mice
(iii) Totterer mice and other seizure-prone mouse strains
(iv) Genetically epilepsy-prone rats

(B) Maximal electroshock
(C) Systemic convulsants
(i) Pentylenetetrazole
(ii) Penicillin
(iii) Other: picrotoxin, bicuculline, methionine, sulfoximine, strychnine

(D) Metabolic derangements

(5) Models for absence seizures:

(A) Thalamic stimulation
(B) Bilateral cortical foci
(C) Systemic penicillin
(D) Gamma-hydroxybutyrate
(E) Intraventricular opiates
(F) THIP (4,5,6,7-tetrahydroxyisoxazolo-4,5-pyridine-3-ol)
(G) Genetic rodent models of absence

(6) Status epilepticus
Large amounts of NMDA, Kainic acid, bicuculline, pentylenetetrazole.

(5) Change in the concentration of neurotransmitters or their metabolites, e.g. glutamate and glutamine.

Plants as a source for new antiepileptic compounds

Table 1 summarized those plants/herbal preparations which have been tested or reported for their *in vivo*/*in vitro* antiepileptic/anticonvulsant activities in the past 30 years. Among those plants tested, a number of them (from different families) are found to possess anticonvulsant activity. While in most cases, the active constituents are yet to be found, for those where the active components are known, they belong to different chemical classes. However, previous studies showed that some natural plant coumarins and triterpenoids exhibit anticonvulsant properties[62, 63].

Plants which warrant further investigations with regards to their anticonvulsant effects are those which have previously been shown to possess the activity, however, the active constituent(s) is not known and the plant is easily available and has low toxicity. From Table 1, plants which fit into the above criteria include: *Albizia lebbek*, *Casimiroa edulis*, *Egletes viscosa*, *Ipomoea stans*, *Piper guineense*, *Piper nigrum*, *Psidium guyanensis*, *Ruta chalepensis*, *Ternstroemia pringlei* and *Tetrapleura tetraptera*.

Clinical data of traditional herbal medicines

Since most of the herbal medicines have been used for a long time without testing, it is very difficult to find sufficient clinical evidence to support their clinical efficacy. In fact, very few clinical studies using herbal medicines were found with regards to the treatment of epilepsy. Four literatures were identified to report the effectiveness of four traditional Chinese herbal medications[56–58] and one Japanese herbal medication[64]. Among these studies, none of them were randomized double blind placebo-controlled clinical trials. Therefore, it is difficult to prove whether the reduction in the seizures was due to placebo effect or spontaneous seizure change. These phenomena also occur in western medicines. For example, a randomized double blind placebo-controlled clinical trial of gabapentin (a new antiepileptic drug) shows about 10% of patients with refractory epilepsy experienced 50% reduction in the seizure.

Four Chinese herbal medications have shown impressive clinical results (see Table 2); however, readers must bear in mind the underlying methodological problems in these studies. These herbal medications are warrant to be subjected to more vigorous clinical trials in the hope of finding more effective treatments. The Japanese treatment was not included in Table 2 since the primary objective of the study was not to test the efficacy in the treatment of epilepsy. Nevertheless, it is interesting to note that the plant *Cynanchum otophyllum* is present in two of these Chinese herbal treatments (treatments 2 and 3B). However, no other studies are found to report its antiepileptic activity. Thus, this plant is certainly of interest for further scientific investigations with regards to its possible antiepileptic effects.

CONCLUSION

The present article reveals that plant species from a wide range of families have been shown to exhibit significant *in vivo*/*in vitro* antiepileptic activities. Among these plants, a number of active components belonging to various chemical classes have been isolated. However, the active components of many of these plants are still remained to be found. Thus, it is the wish of the authors that this review article will stimulate the interests in further investigations into natural products for new antiepileptic agents.

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