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Ethno medicinal plants with anticonvulsant activity through GABAergic mechanism- A review

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Humanity has used immemorial plants for their relieving and healing powers from era and we still depend on their healing properties. Plants with number of active constituents have a direct therapeutic impact on various body organs. Brain is one of major organ linked to various disorders, one of them is epilepsy. Owing to undesirable side effects, high expense and reduced effectiveness of conventional drugs, traditional plants are deemed appropriate for the treatment of epilepsy. The potential of natural products for the treatment of epilepsy can be an excellent alternative for the development of safe and effective anti-epileptic drugs. The present bibliographic review presents the data upto 2021. Plants were screened for citing the research work done for epilepsy, efficacy of plants along with their mechanism of action, plant profile, part used, dose, extract used, toxicity study and model used. Also isolated compounds have been compiled along with their structure. A total of 120 review and research articles of plants which revealed their effective therapeutic effects on epilepsy through GABAergic transmission belonging to families lamiaceae(11), fabaceae(5), zingiberaceae(3), moraceae(3), verbenaceae(3), and apiaceae(2). The data discussed might be useful in formulating new chemical entity for the treatment of epilepsy. The documentation of isolated compounds may provide new drug molecules for market with lesser cost and more efficacy.

Keywords: Anticonvulsant, Epilepsy, GABA, Herbal medicine.

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Introduction

According to WHO, approximately 2.4 million annual cases are reported and about 50 million people are affected with epilepsy worldwide[1]. Clinical study shows that 70% of epileptic patients can live seizure free if properly diagnosed and treated[2]. One of the recent study showed that frequency of active epilepsy is estimated 6.38 per 1000 person and prevalence rate is 61.44 per 100,000 persons/years[3]. Epilepsy causes substantial impact on social, health and quality of life of patients[4]. Epilepsy is a common and usually destructive disorder, identified by the abnormal and periodic discharge of neurons within the brain. Epilepsy is a chronic neurological disorder identified by the unpredictable and periodic occurrence of seizures. Brain is unable to read the message and results in seizures, loss of consciousness, jerking in body muscle, contraction in muscle etc.[5]. The seizures may be due to imbalance between excitatory and inhibitory drive at synapse. Seizures can be inhibited by enhancing Na+ channel inactivation period, enhancing Gama-aminobutyric acid GABA synaptic transmission and by inhibiting the opening of Ca+ channel. GABA and GABA receptors, which mediate antiepileptic effects of many herbal medicines, are one of the important targets well documented in the literature[6].

GABAergic mechanism

Chief inhibitory neurotransmitter in the central nervous system is GABA and is released in about 40% of synapses in the brain. It is synthesized from glutamate by the action of the enzyme glutamic acid decarboxylase[7]. The release of GABA causes hyperpolarizing by acting on $GABA_A$, $GABA_B$, and $GABA_C$ receptors. $GABA_A$ and $GABA_C$ receptors are ligand-gated ion channel. Chloride and bicarbonate are allowed to pass through $GABA_A$ and $GABA_C$ receptor's pores in response to GABA binding[8]. Mammalian $GABA_A$ receptor consist of five independent protein subunits two α, two β and fifth may be γ or δ. $GABA_A$ receptor mediating transient, continuously desensitizing currents at the synapse through α, β and γ subunits, whereas those at extra synaptic sites mediating long lasting and slowly desensitizing through α, β and δ subunits[9].

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$GABA_B$ is G-protein coupled receptor (GPCR) mediates hyperpolarization of potassium channels and decreases calcium entry, therefore exhibiting both inhibitory and excitatory actions[7].

$GABA_C$ receptor contains rho subunit along with α and β subunits and is found in retina, spinal cord, pituitary, and gastrointestinal tract. This receptor is insensitive to bicuculline. As compare to $GABA_A$ receptor, its abundance and distribution is lesser in central nervous system[10].

Various antiepileptic drugs are available for the treatment of epilepsy, but these drugs are unable to provide an ideal therapy as they possess many side effects[11]. So, herbal therapies and complementary medicine are becoming increasingly popular as they have lesser side effects and are effective for long term treatments of seizures. India is a hub of medicinal plants and lots of plant extracts have been used in the treatment of epilepsy in Ayurveda, Unani, and Siddha. Lots of these traditionally used plants have been scientifically explored for the treatment of epilepsy[12]. Therefore, herbs may help in development of antiepileptic drugs in future[13]. The present review provides an overview of traditionally used plants as antiepileptic through GABAergic mechanism.

Review of literature

The present bibliographic review was carried out up to 2021. The data was extracted from various offline sources like standard reference books of pharmacology, Indian Medicinal Plants, Materia Medica, Chinese Herbal Medicine, Nootropic (Medhya) Plants from Ayurvedic Pharmacopoeia. The online information was collected from various databases like Science Direct, Google Scholar, PMC, Research Gate, PubMed, Scopus, Agrocola, Mediline, Shodhganga, and WOS. A total of Total 52 research and 68 review articles from years 2001 to 2022 were thoroughly studied. We also searched about various isolated compounds from plants source useful in epilepsy. In this review, total 12 isolated compounds along with their structures have been compiled. The plants showing antiepileptic activity only through GABAergic transmission were selected for the present review. The data was included based upon:-

1. Plants investigated scientifically for epilepsy treatment with toxicity profile, extract, dose, mechanism of action and models used.
2. Isolated compounds from various plants along with their structure have been explained.
3. Plants native to India, China and other developing countries were mainly considered for the present review.

Role of herbs in the treatment of epilepsy

Medicinal plants are being searched for the treatment of epilepsy due to unwanted side effects, high cost, and less efficacy of synthetic drugs. Plants are cheaper, due to that most of developing countries are dependent on them[14]. List of medicinal plants explored for anti-epileptic activity is shown in Table 1.

Isolated phytoconstituents

Literature survey reveals that several plants phytoconstituents exhibit anti-epileptic activity.

Table 1 — List of medicinal plants investigated for anticonvulsant activity through GABAergic transmission

S. No.	Botanical name	Family	Common name	Part	Acute toxicity	Extract & Dose (mg/kg)	Mechanism of action	Model	Results	Ref.
1	*Ficus religiosa* L.	Moraceae	Ashwattha Tree	R	Safe up to 2000 mg/kg	Aq (25, 50 and 100)	Enhance GABA through GABAergic pathway	PTZIC	Dose-dependent effect was observed & extract showed complete inhibition of onset of seizures induced by PTZIC	15
2	*Trachyspermum ammi* L.	Apiaceae	Ajowan caraway	S	LD_{50} 831 mg/kg	M (50)	Enhance GABA neurotransmission at $GABA_A$ receptor and increasing the chloride ion channel opening	SIC	Effective protection against seizures, percentage inhibition was 42.8 % as compared to control	16, 17

(*Contd.*)

Table 1 — List of medicinal plants investigated for anticonvulsant activity through GABAergic transmission (*Contd*.)

S. No.	Botanical name	Family	Common name	Part	Acute toxicity	Extract & Dose (mg/kg)	Mechanism of action	Model	Results	Ref.
3	*Valeriana officinalis* L.	Valerianaceae	Garden heliotrope	R	DNF	Aq (200, 500 and 800)	Valepotriates and valerenic acid present in extracts showed $GABA_A$ agonistic effect	SKP	Extract showed maximum protection at 500 mg/kg in temporal lobe epilepsy	18
4	*Cymbopogon winterianus* Jowitt.	Poaceae	Java citronella	L	LD_{50} 1953.8 mg/kg	Eo (50, 100 and 200)	GABAergic mechanisms, deteriorated autoregulation of glutamate release	PIC	Dose-dependent effect observed, and extract showed its maximum protection at 200 mg/kg	19, 20
5	*Rosmarinus officinalis* L.	Lamiaceae	Rosemary	F and L	Safe up to 2000 mg/kg	M (50, 100, 500 and 1000)	Increase GABA levels in the midbrain region	PIC	Maximum anticonvulsant activity was at 500 mg/kg dose and delayed the death rate but didn't change in mortality rate	21
6	*Curcuma longa* L.	Zingiberaceae	Rhizoma curcumae	Wp	Safe up to 3000 mg/kg	Eo (100)	Facilitation of $GABA_A$ receptor, facilitation of recombinant $GABA_A$ receptor and enhancement of phasic and tonic GABAergic inhibition	PIC	Effective protection against basal locomotor activity and chemically induced seizure activity	22
7	*Passiflora incarnata* L.	Passifloraceae	Maypop	L, F and Fr	Safe up to 2000 mg/kg	Ha (0.05, 0.1, 0.2 and 0.4)	Enhancement of GABAergic pathway	PTZIC	Mortality and seizure protection was 100% at 0.4 mg/kg	23
8	*Bryonia alba* L.	Cucurbitaceae	White bryony	DNF	250 mg/kg was found safer	E DNF	Moderate affinity for benzodiazepine site at GABA receptor	IVBA (Binding of flumazenil)	Seizures were treated	24, 25
9	*Caesalpinia bonducella*	Fabaceae	Fever nut	S	LD_{50} 3000 mg/kg	Pe (400, 600 and 800)	Blockage of chloride channel linked to $GABA_A$ receptor and inhibition entry of chloride channel in the brain, thus inhibit GABA neurotransmission	PTZIC	Higher dose showed significant effect on tonic clonic seizures	26
10	*Cannabis sativa* L.	Cannabaceae	*Marijuana*	Wp	LD_{50} 666 mg/kg on intragastric route	Ro (200 and 300)	Inhibition of the release GABA and glutamate	EIM	Maximum protection was observed at 300 mg	27, 28

(*Contd*.)

Table 1 — List of medicinal plants investigated for anticonvulsant activity through GABAergic transmission (*Contd.*)

S. No.	Botanical name	Family	Common name	Part	Acute toxicity	Extract & Dose (mg/kg)	Mechanism of action	Model	Results	Ref.
11	*Mentha piperita* L.	Lamiaceae	Peppermint	L	Safe up to 1500 mg/kg	Ha (400, 600 and 800)	Extract prevented seizures by increasing GABA levels in the midbrain, limonene by affecting GABAA receptors and increasing GABA concentration `	PTZIC	Seizures inhibition was observed at 800 mg/kg (percentage inhibition 100%)	29, 30
12	*Lavandula angustifolia* Mill.	Lamiaceae	True laven der	Ap	Safe up to 2000 mg/kg	Aw (100, 200 and 400)	The effects of linalool on binding of N-methyl-D-Aspartate (NMDA) glutamate antagonist and GABAA agonist	PTZIC	Increase in seizure latency as well as protection effect was 66%	31,32
13	*Bunium persicum* Boiss.	Apiaceae	Black caraway	S	Safe up to 4000 mg/kg	M (500, 1000, 2000, 3000 and 4000)	Act through GABAergic mechanism and increase opening of chloride channel	PTZIC	Methanol extract of the plant increased the onset time of clonic and tonic convulsions at dose 3000 mg	33
14	*Salvia miltiorrhiza* Bge.	Lamiaceae	Red sage	R	Safe up to 64000 mg/kg	A (0.1, 1 and 10)	A propensity to interact with pathways irrelevant to GABA and related agonists	PTZIC	Dose-dependent effect observed maximum percentage inhibition at 10 mg	34, 35
15	*Zingiber officinale* Rosc.	Zingiberaceae	Red sage	R	Safe up to 5000 mg/kg	E (25, 50 and 100)	Inhibits chloride ion channel of $GABA_A$ receptors	PTZIC	Doses were able to inhibit generalized tonic clonic seizures in dose dependent manner	36
16	*Zizyphus jujube* Mill.	Rhamnaceae	Adraka R	Fr	Safe up to 5000 mg/kg	M (100, 250, 500 and 1000)	Inhibition of glutamate-induced over excitation, a decrease in synaptic release of glutamate, inhibits effect of GABA and reduce the excitation	PTZIC	1000 mg/kg dose exhibited 100% protection against generalized tonic–clonic seizures in the PTZIC and 66.7% protection against tonic hindlimb extension in the MESIC	37-39

(*Contd.*)

Table 1 — List of medicinal plants investigated for anticonvulsant activity through GABAergic transmission (*Contd*.)

S. No.	Botanical name	Family	Common name	Part	Acute toxicity	Extract & Dose (mg/kg)	Mechanism of action	Model	Results	Ref.
17	*Annona senegalensis* Per.	Annonaceae	Wild custard apple	R and B	LD_{50} 3000 mg/kg	Aq (200, 400 and 800)	Enhance GABA neurotransmission	MESIC & PTZIC	Extract prolonged the latency of convulsions and maximum inhibition was observed at 200 mg	40, 41
18	*Bryophyllum Pinnatum* Lam.	Crassulaceae	Ghamari	L	Safe up to 2000 mg/kg	Aq (50, 100 and 200)	Increase brain GABA content	PCTIC	No change was observed at 50 mg/kg but at 200 mg/kg dose it showed maximum anticonvulsant effect	42
19	*Kalanchoe crenata* Andr.	Crassulaceae	Neverdie	L	Safe up to 1000 mg/kg	M (150 and 300 and 600)	An antagonism of GABA synthesis	PTZIC	Increased latency period in seizures and maximum inhibition at 600 mg	43, 44
20	*Bacopa monnieri* L.	Plantaginaceae	*Brahmi*	St	Safe up to 1000 mg/kg	Aq, E and A (100, 200 and 300)	GABA agonist action	PTZIC	Dose-dependent effect observed, and maximum protection was seen at 300 mg/kg dose	45
21	*Rosa damascena* Mill.	Rosaceae	Damask rose	L	Safe up to 2000 mg/kg	Eo (250, 500, 750 and 1000)	Act on $GABA_A$ receptors in the brain of rats/ enhancing the effects of benzodiazepines on GABA receptors	PTZIC	750 mg/kg dose delays the start of epileptic seizures	46
22	*Argyreia speciose* Lour.	Convolvulaceae	Hawaiian baby woodrose	R	Safe up to 2000 mg/kg	Ha (100, 200 and 400)	Glutamatergic transmission inhibition	PTZIC	Dose-dependent effect observed and maximum protection at both dose 200 and 400 mg/kg	47
23	*Boerhaavia diffusa* L.	Nyctaginaceae	Punarnava	R	Safe up to 2000 mg/kg	M (1000, 1500 and 2000)	By inhibiting the activity of GABA at $GABA_A$ receptors	PTZIC	Dose-dependent result was observed	48
24	*Dorstenia arifolia* L.	Moraceae	Grendelion	Ap	Safe up to 5000 mg/kg	Ea (10, 30 and 50)	Act through GABAergic mechanism	PTZIC	A significant decrease of the incidence of clonic convulsions and maximum inhibition was at 50 mg	49

(*Contd*.)

Table 1 — List of medicinal plants investigated for anticonvulsant activity through GABAergic transmission (*Contd.*)

S. No.	Botanical name	Family	Common name	Part	Acute toxicity	Extract & Dose (mg/kg)	Mechanism of action	Model	Results	Ref.
25	*Sutherlandia frutescens* R. BR.	Fabaceae	Bitterblaar	Ap	Safe up to 1600 mg/kg	Aq (25, 50, 100, 200 and 400)	Enhancing GABAergic transmission in brain	PTZIC	Aqueous extract (50–400 mg/kg) produced dose-related, significant protection (P <0.05–0.001) of the mice against PTZ-induced seizures	50
26	*Scutellaria lateriflora* L.	Lamiaceae	Blue skullcap	R	DNF	Aq (30, 60, 90 and 150)	Showed high affinity for the benzodiazepine binding site of $GABA_A$ receptor	PTZIC	The latency to seizure onset was significantly increased and maximum protection against observed at 90 mg	51
27	*Lippia citriodora* Kun.	Verbenaceae	Lemon verbena	L	Safe up to 2000 mg/kg	E (200, 400 and 800)	Antagonist of GABA /benzodiazepine receptor complex	PTZIC	800 mg/kg made the latency of seizure longer, compared to other two dose	52
28	*Gemlina arborea* Roxb.	Verbenaceae	Goomar teak	St	Safe up to 2000 mg/kg	M (250 and 500)	Involvement of GABAergic /by inhibiting the activity of GABA at $GABA_A$ receptor.	PTZIC	Percentage protection was 60% and 80% at dose 250mg and 500 mg dose respectively	53
29	*Alpinia officinarum* Han.	Zingiberaceae	Lesser galangal	R	LD_{50} 7500-7700 mg/kg	Ha (200, 400 and 600)	Agonistic effect on GABAergic transmission	PTZIC	No effect was observed at 200 and 400 mg but at dose of 600 mg it was totally 100% protection against seizures	54, 55
30	*Allium cepa* L.	Amaryllidaceae	Bulb onion	DNF	Safe up to 2000 mg/kg	M (200 and 400)	Increase level of GABA modulation in whole brain	IIC	Extract (200 and 400 mg/kg) showed significant reduction in the duration of hind limb extensor phase	56
31	*Butea monosperma* Lam.	Fabaceae	Bastard teak	St	Safe up to 2000 mg/kg	M (100, 200 and 300)	Interacts with GABAergic neurotransmission basically through $GABA_A$ mediated action	PTZIC and MESIC	Extract delayed all the parameters like onset of jerk, straub tail, onset of clonus and extensor phases in a dose dependent manner	57

(*Contd.*)

Table 1 — List of medicinal plants investigated for anticonvulsant activity through GABAergic transmission (*Contd*.)

S. No.	Botanical name	Family	Common name	Part	Acute toxicity	Extract & Dose (mg/kg)	Mechanism of action	Model	Results	Ref.
32	*Antiaris toxicaria* Pers.	Moraceae	Upas tree	B	Safe up to 3000 mg/kg	Aq (200, 400 and 800)	By interacting with the $GABA_A$ receptor significantly increase in GABA level	PIC	Dose produced significant effect on the latency to myoclonic jerks	58, 59
33	*Benkara malabarica* L.	Rubiaceae	Cholakara	R	Safe up to 500 mg/kg	M (25 and 50)	Extract possesses GABA-T inhibitory activity / GABA-T decreases the level of GABA in the brain and increases the level of l-glutamate	SIC and IIC	Effect of the extract was dose dependent.	60
34	*Datura metel* L.	Solanaceae	Devil's trumpet	L	Safe up to 2000 mg/kg	E (200 and 400)	By enhancing the GABA in GABAergic pathway	PTZIC	The extract significantly delayed the onset of myoclonic jerks and reduction in the duration of tonic convulsions at doses of 200 mg/kg and 400 mg/kg	61
35	*Pseudospondias microcarpa* A. Rich.	Anacardiaceae	Ochol	DNF	Safe up to 3000 mg/kg	E (30, 100, 300, 1000 and 3000) Vo (35)	GABAergic stimulation	PTZIC	Dose dependent result was observed	62, 63
36	*Acorus tatarinowii* Schott.	Acoraceae	Sweet flag	DNF	Safe up to 350 mg/kg	M (25, 50 and 75)	Enhance the level GABA in brain	KAIS	Dose given to animal showed significant effect on seizures	64
37	*Corchorus olitorius* L.	Malvaceae	Jute mallow	St	Safe up to 5000 mg/kg	M (50 and 75)	Increase GABA level in brain	SIC	Inhibition of seizures was observed in dose dependent manner	65, 66
38	*Albizzia lebbeck* Benth.	Fabaceae	Lebbek tree	L	Safe up to 5000 mg/kg	E (250, 500, 750 and 1000)	Enhance GABA level in brain	PTZIC	Dose dependent result was observed	67
39	*Spathodea campanulata* P. Beauv	Bignoniaceae	Nandi flame	L	LD_{50} 4500 mg/kg	E and M (300) E (100 mg/kg)	Enhancement in GABA inhibitory action	PTZIC	The extract reduced the duration of PTZ-induced convulsion in a dose-dependent manner	68

(*Contd*.)

Table 1 — List of medicinal plants investigated for anticonvulsant activity through GABAergic transmission (*Contd.*)

S. No.	Botanical name	Family	Common name	Part	Acute toxicity	Extract & Dose (mg/kg)	Mechanism of action	Model	Results	Ref.
40	*Lippia alba* Mill.	Verbenaceaeae	Matgrass	DNF	Safe up to 4000 mg/kg	O (5,10, 20, 40 mg/kg)	Inhibition of GABA binding and GABA uptake	PTZIC	Dose given to animal showed significant effect on seizures	69, 70
41	*Valeriana edulis* ssp. Procera	Valerianaceae	Valeriana mexicana	R	DNF	(125, 250, 500 mg/kg)	$GABA_A$ and cannabinoid CB_2 receptor Involvement	PTZIC	Reduction of excitatory activity in dose dependent manner	71
42	*Zhumeria majdae* (Rech.)	Lamiaceae	Mohrkhosh	L	3.09 g/kg; 3.94 g/kg	O (5,10, 20,40 mg/kg)	GABAergic mechanism and the NO signaling pathway	PTZIC	Increased chronic seizure threshold and latency while reduced frequency of convulsions and mortality	72
43	*Morus Nigra* L.	Moraceae	Black mulberry	L	Safe upto 2000 mg/kg	L (125, 250 and 500 mg/kg)	Potentiation of GABAergic and Glycinergic activity	SIC	Delayed latent of seizures, decrease in frequency and jerk's duration	73

Abbreviations: IIC (Isoniazid induced convulsion) - SIC (Strychnine induced convulsion) - SKP (Surgical and kindling procedure) - PIC (Pilocarpine induced convulsion) - PTZIC (Pentylenetetrazol induced convulsion) - IVBA (*In vitro* binding assay) - EIM (Electroshock in mice) - MESIC (Maximal electroshock induced convulsion) - PCTIC (Picrotoxin induced convulsion) - KAIS (Kianic acid induced seizure)
Aq (Aqueous), M (Methanol), Eo (Essential oil), E (Ethanol), Pe (Petroleum ether), Ro (Realm oil), Ha (Hydroalcoholic), Aw (Aromatic water), A (Acetone), Ea (Ethylacetate), Vo (Volatile oil)
R (Root), S (Seed), L (Leaves), F (Flower), Wp (Whole plant), Fr (Fruit), Ap (Aerial part), St (Stem), O (Oil)
DNF (Data not found), GABA (Gamma-aminobutyric acid)

Phytochemicals are plant-derived chemicals used to identify number of secondary metabolic compounds present in the plants[74]. Various phytoconstituents such as alkaloids, terpenes, triterpenoids, lipids, flavonoids etc. have been documented to possess anticonvulsant action (Fig. 1).

Tanshinone IIA is the chief constituent of plant *Salvia miltiorrhiza* (Family: Lamiaceae) showing anticonvulsant activity. Plant is also known as Danshen or Chinese red sage and is traditionally used in the Chinese medicine for treatment of cardiovascular, cerebrovascular, and neurological disorders. Tanshinone IIA was used to treat convulsions induced by PTZ-induced seizures animal model by agonizing the action of $GABA_A$ receptor[34].

Limonene was isolated from plant *Mentha piperita* (Family: Lamiaceae). This plant is traditionally used as tranquilizer, stomach booster, pain reliever and anticonvulsant. Limonene was found to increase GABA concentration in PTZ induced convulsion animal model specially by affecting $GABA_A$ receptor[29].

(±) 3-Menthone is main chemical constituent of *Mentha piperita* (Family: Lamiaceae). *Mentha piperita* is found in most region of Iran (in northern and northeastern Iran). Several other components of peppermint are also isolated (±) 3-menthone, methyl acetate, menthol, neomenthol and 1,8 cineole. (±) 3-menthone was evaluated for anticonvulsive activity at dose 30, 100, and 300 mg/kg by using electroconvulsiometer and PTZ-induced convulsions. The compound was found very effective in elevating the level of GABA in mid brain[29,62].

Liriodendrin is the main chemical constituent of *Boerhaavia diffusa* (Nyctaginaceae :Family) and has been isolated from the methanol root extract of *Boerhaavia diffusa*. Many other components like punarnavine, boeravinones A–F, hypoxanthine 9-larabinofuranoside, ursolic acid, punarnavoside and punarnavoside have also been isolated from this plant.

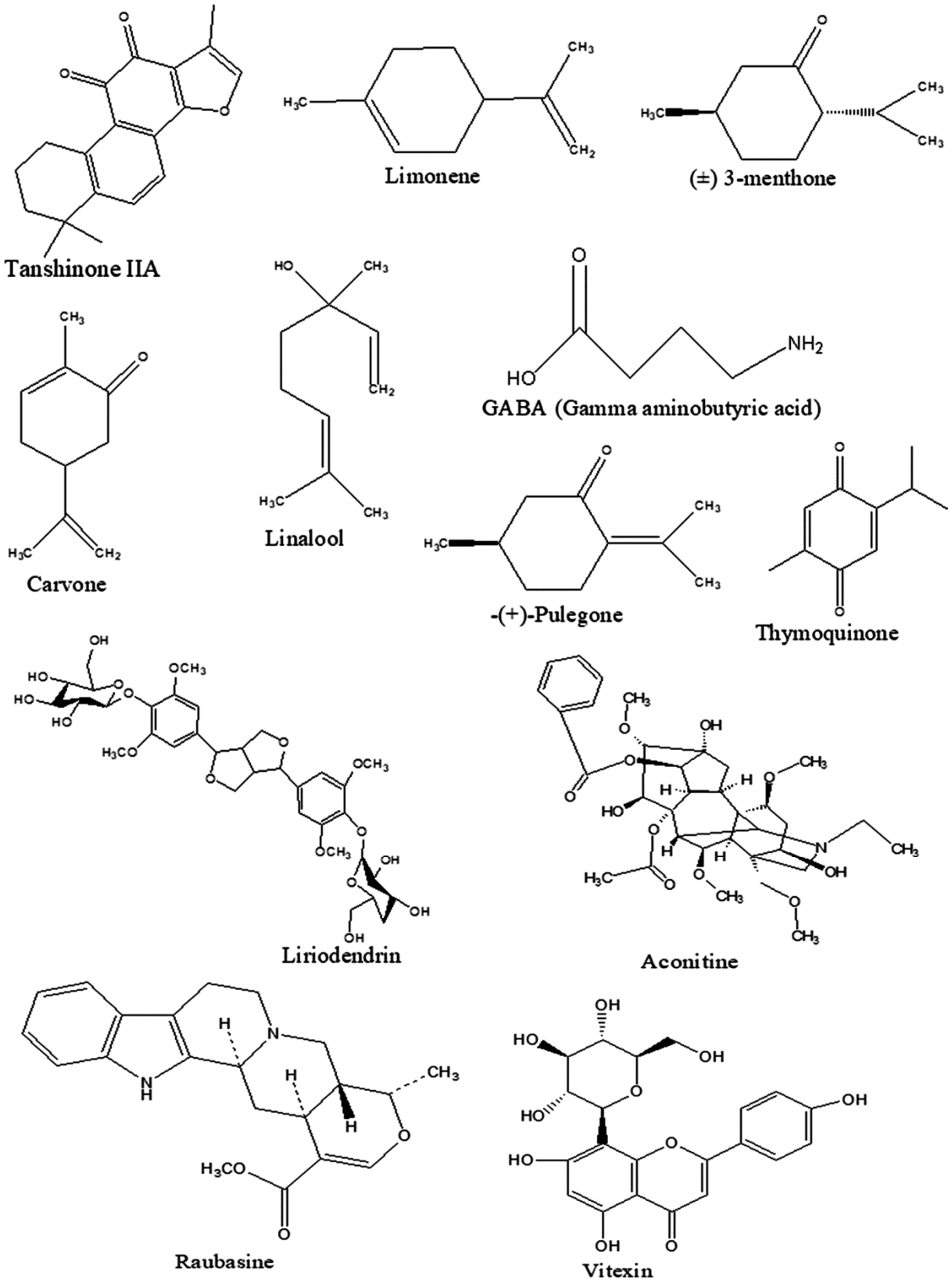

Fig. 1 — Structure of isolated compounds for anticonvulsant activity.

Liriodendrin shows anticonvulsant effect by blocking calcium channels. PTZ-induced seizures animal model was used for evaluation of anticonvulsive activity and showed very good activity[48,75].

Linalool is one of the main constituents of *Lavandula angustifolia* (Family: Lamiaceae). Plant also possesses other pharmacological activities like anti-nociceptive, analgesic and anti-inflammatory. The anticonvulsant effect of linalool has been studied on mouse cortical membranes through binding of [3 H]MK801 and [3 H] muscimol. The mechanism of antiepileptic action was N-methyl-Daspartate (NMDA) glutamate antagonism and $GABA_A$ agonism[76].

GABA (Gamma aminobutyric acid) was isolated from the plant *Sutherlandia frutescens*) :Family Fabaceae). Plant also contains other bioactive chemical constituents like amino acid, lcanavanine, pinitol, asparagines and some saponins. GABA inhibits seizures induced by PTZ and PCT-induced seizures by acting on GABA receptor or indirectly the GABAnergic neurotransmission in the brain[50].

-(+)-Pulegone was obtained from the plant *Mentha pulegium* (Family: Lamiaceae). Anticonvulsant effect of -(+)-pulegone was evaluated by using 300 mg/kg dose *i.p.* The anti-convulsant action of pulegone was through increase in the latency of PTZ-induced convulsions and its efficacy as anticonvulsant was similar to that of standard drug diazepam[77].

Thymoquinone is main active chemical constituent of *Nigella sativa* (Family: Ranunculaceae). A dose of 150 mg/kg of thymoquinone show protection in bicuculline-induced seizures through GABAergic transmission pathway probably through $GABA_A$ receptor mediation[78].

Carvone is one of the major components (38%) of *Calamintha officinalis* (Family: Lamiaceae). It is used as flavoring agent in cosmetics and toothpaste. Carvone also possess other activities like antimicrobial, antifungal, antiseptic, cicatrizant etc. It reduces locomotor activity in animals and increase latency periods in PTZ-induced seizures[79].

Aconitine is the major component of *Aconitum napellus* (Family: Ranunculaceae) and showed anticonvulsant effect at doses 0.1 and 1 µm in convulsions induced by PTZ and bicuculline induced convulsion models by blocking $GABA_A$ receptor mediated inhibition[80].

Raubasine is obtained from the plant *Rauwolfia serpentine* (Family: Apocynaceae). It was used to evaluate anticonvulsant activity in PTZ and bicuculline induced seizures models at 40.6 mg/kg dose. The compound exhibited very good antiepileptic activity through action on benzodiazepines as agonist[81].

Vitexin was evaluated for anticonvulsant activity at doses 100 and 200 µm in PTZ (90 mg/kg, *i.p*) induced seizures in rats. Vitex was found to increase the seizure onset time by interacting with $GABA_A$ benzodiazepine receptor complex[82].

Magnolol and honokiol were isolated from *Magnolia officinalis* (Magnoliaceae), a deciduous tree commonly known as magnolia plant. Magnolol and honokiol were evaluated for anticonvulsant activity in PTZ and ethylketopentenoate (EKP) Zebra Fish models. Both the compounds were found to be efficacious for antiepileptic activity[83].

Discussion

Herbal medications are currently the most usual approach to complementary and alternative medications, which play an important part in developing the new drug entity with lesser cost and side effects. In this review, a total of 120 review articles and research papers were reviewed thoroughly. About 40 articles were reviewed for the isolated compounds for antiepileptic activity along with their structure. 120 articles were checked for citing the research work done for epilepsy, efficacy of plants along with their mechanism of action, plant profile, part used, toxicity study, dose, extract used, and model used in research study. The plants reviewed for our research were mainly from the families moraceae(3), apiaceae(2), valerianaceae(1), poaceae(2), lamiaceae(11), zingiberaceae(3), passifloraceae(1), cucurbitaceae(1), fabaceae(5), cannabaceae(1), rhamnaceae(1), annonaceae(1), crassulaceae(2), plantaginaceae(1), rosaceae(1), convolulaceae(1), nyctaginaceae(2), verbenaceae(3), amaryllidaceae(1), rubluceae(1), solanaceae(1), anacordiaceae(1), acoraceae(1), malvaceae(1), bignoniaceae(1), ranunculaceae(2) and apocynaceae(1). From the above data it is shown that maximum number of plants belonged to families lamiaceae(11), fabaceae(5), zingiberaceae(3), moraceae(3), verbenaceae(3) and apiaceae(2). In above list, most commonly animal models used were pentylenetetrazol, isoniazid, strychnine and picrotoxin induced convulsions. From the literature survey it was observed that various parts of plants like roots, seeds,

leaves, bark, flowers, fruits, aerial parts and stem were used. In this review, the authors mainly focused on the plants which revealed their action through GABAergic transmission. From the above data, it was also observed that maximum research is going on in developing countries. It is figured out that this review could be a huge assist to natural product researcher to select scientifically explored plants for further isolation of compounds that can be used to conduct clinical studies, so that a cheaper and side effects free novel medicines could be provided to society.

Conclusion

The potential of natural products for the treatment of epilepsy could be an excellent alternative for the development of safe and effective anti-epileptic drugs. The data discussed might be useful in formulating new chemical entity for treatment of epilepsy. The isolated compounds mentioned in the review may provide new drug molecules with lesser cost and more efficacy.

Conflict of interest

The authors do not have any conflict of interest.

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