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REVIEW ARTICLE **OPEN ACCESS**

Role of Pentylenetetrazole (PTZ) in preclinical research for the biological screening of antiepileptic medicinal plants

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ABSTRACT
The Epilepsy is a disorder in the brain reflected by continuing disposition to produce epileptic seizures through the neurobiologic, cognitive, psychological, and social significances of this illness. Nowadays many of the synthetic drugs are available commercially to treat epilepsy. However synthetic drugs associated with side effects, adverse effect and cost effective. So that alternative medicine like herbal and herbal extracts plays the important role in treatment of epilepsy. The scientific evidence of traditional medicine is important in society for the knowledge of the treatment. Pentylene tetrazole (PTZ) is one of the chemical which is used to screening of antiepileptic activity in animal models. This review is focused on importance of PTZ in preclinical research in details. This review will very useful for researcher to study the antiepileptic activity of newer drugs/herbals.
Keywords: *Epilepsy, traditional medicine, Animal model, Seizure and Convulsion.*

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INTRODUCTION

Epilepsy is known as seizures. These seizures are transitory ciphers and/or indications of irregular, extreme or synchronous neuronal activity in the brain [1]. It is a disorder of the brain considered by continuing disposition to produce epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this illness. The description of epilepsy involves the incidence of at smallest one epileptic seizure. It is the most mutual serious brain disorder universal through no age, racial, social class, neither national nor geographic limitations [2]. Nearly 50 million people presently live with epilepsy universal. The probable amount of the general populace with vigorous epilepsy (i.e. enduring seizures or with the need for treatment) at assumed time is among 4 and 10 per 1000 persons. Though, some readings in low- and middle-income nations propose that the amount is plentiful, among 7 and 14 per 1000 persons [3]. Presently several of the antiepileptic drugs existing commercially which is list out in Table 1.

Table 1: Classification of antiepileptic drugs

S. No	Classification	Drug name
1	Barbiturate	Phenobarbitone
2	Deoxybarbiturate	Primidone
3	Hydantoin	Phenytoin Fosphenytoin
4	Iminostilbene	Carbamazepine Oxcarbazepine
5	Succinimide	Ethosuximide
6	Aliphatic carboxylic	Valproic acid acid (sodium valproate) Divalproex
7	Benzodiazepines	Clonazepam, Diazepam, Lorazepam, Clobazam
8	Phenyltriazine	Lamotrigine
9	Cyclic GABA Gabapentin analogues	Pregabalin
10	Newer drugs	Topiramate, Zonisamide, Levetiracetam Vigabatrin, Tiagabine, Lacosamide

DISADVANTAGES OF SYNTHETIC DRUGS

The synthetic drugs are having the following disadvantages

- ☑ Synthetic drugs associated with adverse effect such as Diplopia, dizziness, headache, ataxia, nystagmus, skin rashes, hyponatremia, aplastic anemia, agranulocytosis, weight gain, Stevens–Johnson syndrome, osteomalacia, hepatoxicity, teratogenicity, etc.
- ☑ Cost effective is high (Economical burden).

IMPORTANCE OF MEDICINAL PLANTS IN ANTIEPILEPTIC ACTIVITY

The medicinal plants are the alternative to the synthetic drugs these are the medicinal plants are commonly having the less side effects and also less cost effect. These are the medicinal plants used in traditionally in Ayurveda and siddha. Now a day's scientist has great knowledge to scientific reasons for using of these medicinal plants in ailment. In scientific validation of herbal medicine, screening of biological activity is plays the important role. Biological screening of medicinal plants can achieved by *in vitro*, *Ex vivo*, *In silico* and *in vivo* models.

BIOLOGICAL SCREENING OF ANTIEPILEPTIC MEDICINAL PLANTS

The *in vitro* study is achieved by cell lines (DNA fragmentation study, gene expression study), *in silico* is achieved by using software (Molecular docking for binding site of receptor, ADME parameters) and *in vivo* model is achieved in laboratory animals such as rat, mouse [4], zebrafish and guinea pigs using various induction methods (Maximal electroshock, Pentylene tetrazole, Lithium-pilocarpine, Lithium-methomyl, Isoniazid induced seizures).

ROLE OF PENTYLENE TETRAZOLE (PTZ) IN BIOLOGICAL SCREENING OF MEDICINAL PLANTS

Many of the chemicals used for the induction of seizures in animals but the PTZ plays the important role in screening of antiepileptic drugs. So that current review is focusing on PTZ induced animal model. The diagrammatic representation of PTZ induced animal model is shown in Figure 1.

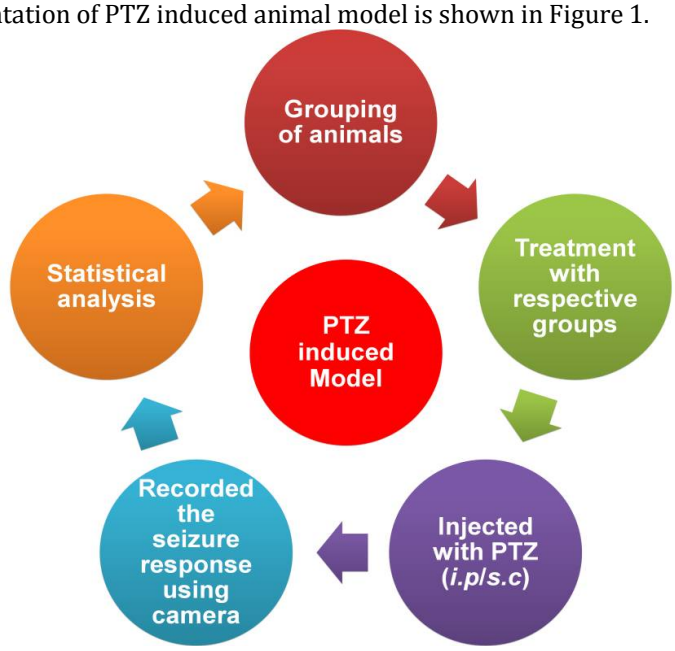

Figure 1: PTZ animal model for screening of antiepileptic activity

Grouping of animals

The grouping of animals (Rat/ Mice/ Guinea pig) is important in the preclinical research the grouping is used for the comparison of activity. The animals are commonly grouped as following groups and each group contains minimum of 6 animals each for the statistical purpose [5].

Group I: This group is normal group (Commonly this group is not undergoes any induction or treatment which is only received distilled water/vehicle)

Group II: This group is disease control group (This group is not treated with any of the drugs only induced with PTZ at the time of induction)

Group III: This group is standard group (This group is treated with reference standard antiepileptic drugs such as Phenobarbitone, Primidone, Phenytoin, Fosphenytoin, Carbamazepine, Oxcarbazepine, Ethosuximide, Valproic acid acid, etc., before 30/60 min of the induction of PTZ)

Group IV: This group is test group (This group is treated with test drugs such as herbal, herbal extracts, herbal fractions and isolated compound before 60/30 min of the induction of PTZ)

Induction of epilepsy by PTZ

PTZ is a central nervous system (CNS) stimulant with convulsive properties which is widely used to study the antiepileptic activity of medicinal plants [6]. PTZ is known as a non-competitive gamma-aminobutyric acid (GABA) antagonist at the GABAA receptor, thereby it causes convulsing effect, but the exact molecular mechanism is not entirely understood, which includes the exact binding site of PTZ at GABAA receptor complex and other sites of actions [7]. About 30 min/ 60 min after the treatment of respective group of animals (some researchers pretreated test drugs for 7 or 14 days) are injected (subcutaneously or intra-peritoneal) with PTZ.

Recording of Seizure response

After the injection of PTZ each animal is placed into an individual plastic cage for observation lasting 30 min. The survival camera is fitted to the watching of seizures response. The following phases were recorded [8, 9].

Phase 0: No response
Phase 1: Ear and facial twitching
Phase 2: Myoclonic body jerks
Phase 3: Clonic forelimb convulsions
Phase 4: Generalized clonic convulsions, turning onto one side position
Phase 5: Generalized clonic-tonic convulsions (or death within 30 minutes)
Phase 6: Mortality [10]

Statistical analysis

The epilepsy parameters are compared by One-way ANOVA followed by the Student–Newman–Keuls test/ Dunnet test/ Turkey test. Differences were considered to be statistically significant ($P < 0.05$/ $P > 0.01$). The commonly normal group is compared with negative group, negative group is compared with the all treatment groups (Test and standard) and test group is also compared with normal and standard group (which shows no significant difference). The significant differences between the groups confirm the activity of newer drugs.

The type of animal, different doses, parameters used in the PTZ induced epileptic animal model is shown in Table 2.

Table 2: Antiepileptic activity of medicinal plant using PTZ induced animal model

Plant name	Extract/Part	Treatment dose (*p.o*)	Animal used	PTZ dose (*i.p*)	Parameters	Author
Myrothamnus moschatus	Essential oil of the aerial parts	0.1–0.8 ml/kg	Wistar rats either sex (200–250 g)	60 mg/kg	Latency period of Seizure, Duration of epileptic Seizure, Mortality	[11]
Datura metel	Ethanol/ leaf	200 mg/kg and 400 mg/kg	Swiss albino mice weighing 25 to 30 gm	80 mg/kg	Latency, Duration of convulsion (sec)	[12]
Benincasa hispida	Methanol/ fruit	300mg/kg	Male Swiss albino mice(18-25g)	75 mg/kg	Onset of seizures, Death Time	[13]
Psidium guajava	Ethanol/ leaf	200 mg/kg, 400 mg/kg	Albino mice (25-30gms) of either sex	70 mg/kg	Seizure latency	[14]
Lawsonia inermis	Methanol/ leaves	200 mg/kg and 400 mg/kg	albino rats 150-250 g each of either sex	80 mg/kg	Onset of clonic convulsion Duration of clonic convulsions (sec)	[15]
Cyperus rotundus	Ethanol/ rhizomes	100 mg / kg	albino rats of either sex weighing between 150 to 220 g	80 mg/kg	Duration of Convulsions Mortality	[16]
Artesunate	Isolated compound	36.4 and 72.8 mg/kg I.P.	Swiss albino mice of either sex 20–25 g	30 mg/kg *s.c*	Duration of convulsions	[17]
Cassia fistula	Methanol/ seeds	100 mg/kg	Swiss albino	60mg/kg	Onset of Jerks,	[18]

		200mg/kg	mice weighing (20-30g)		Duration of convulsion	
Ipomea reniformis	Methanol/ whole plant	100, 200, 300 mg/kg	Swiss albino mice of either sex 25–30 g	80 mg/kg sc	Onset of clonic convulsion, mortality	[19]
Trachyspermum ammi	Ajwain oil	75mg/kg	male Swiss albino mice weighing about 20-30 g	60 mg/kg	Onset of myoclonus Onset of clonic seizures	[20]
Anogeissus latifolia	Ethanol/ stem bark	200, 400, and 600 mg/kg,	Swiss albino mice of either sex (20–30 g)	80 mg/kg	Animals protected against seizures, Duration of clonic convulsion	[21]
Sapindus emerginatus	Methanol/ Fruits	200 and 400 mg/kg	Male albino wistar rats weighing between 180-220 g	60 mg/kg	Serotonin, Nor - adrenaline and Dopamine	[22]
Asparagus adscendens	Hydro ethanol/ root	25, 50, 100 and 200 mg/kg *ip*	Swiss albino mice weighing 20-30 g	75 mg/kg.	Latency to tonicclonic Convulsions Mortality	[23]
Hibiscus vitifolius	Ethanol/ leaves	(200, 400 and 600 mg/kg)	Wistar albino rats (150-200g)	60 mg/Kg)	clonic convulsions, mortality	[24]
Musa sapientum	Aqueous/ stem	100 mg/kg,	Swiss albino mice of either sex 25 and 30 g	30 mg/kg, *s.c.*, (Thrice a week for 21 days) 60 mg/kg (*i.p.*)	clonic convulsions	[25]
Terminalia chebula	Ethanol/ Fruits	200 and 500 mg/kg	Swiss mice of either sex 25-30 g	80 mg/kg., *s.c*	Latency of tonic convulsion	[26]
Tricosanthes dioica	Aqueous/ fruits	100, 200 and 400 mg/kg	Albino mice(20-25g) of either sex	80 mg/kg	Seizure duration	[27]
Desmodium Triflorum	Ethanol/ leaves	400 and 800 mg/kg	Swiss albino mice of either sex (18-20 g)	65 mg/kg	Duration of Convulsion, Mortality	[28]
Pinus roxburgii	ethanol extract, Chloroform, n-Hexane, n-Butanol and Ethylacetate fraction stem bark	250 and 500 mg/kg	adult albino wistar rats of either sex, 150-200 g	60 mg/kg	myoclonic jerks, Total duration of seizure	[29]
Tephrosia purpurea	Ethanol/stem bark	200 mg/kg and 400 mg/kg	Not specified	60 mg/kg., *s.c,*	Onset of seizures	[30]
Acalypha fruticosa	Chloroform/ aerial parts	30, 100 and 300 mg/kg	Swiss albino mice (25-30 g) of either sex	75 mg/kg,	Duration of convulsion	[31]
Viola tricolor	Leaves/ ethanol	100, 200, and 400 mg/kg	Male albino mice 22 and 28 g	100 mg/kg	Latency of seizures	[32]
Punica granatum	Petroleum ether, methanolic, aqueous/ leaves	50, 100, 200 and 400 mg/kg)	Inbred Swiss albino mice (25-30 g)	80 mg/kg	Onset of clonus, Onset on tonic, death rate	[33]
Biophytum sensitivum	Ethanol/ leaves	50, 100 and 200 mg/kg	Swiss albino mice 20 25gm	80 mg/kg	Onset time, Percentage inhibition of convulsions	[34]
Ficus sur Forssk	Ethanol/ Stem-bark	400 and 800 mg kg ,	Albino mice of both sexes	90 mg kg , i.p.	latency to convulsion	[35]

			20-25 g		and protection from seizures	
Carissa carandas	Ethyl alcohol/ root	100, 200 and 400 mg/kg	Swiss mice of either sex, 25-30 g	90 mg/kg	Latency of tonic convulsion	[36]
Pistacia integerrima	Methanol	50mg/kg, 100mg/kg, and 200 mg/kg	Adult 4-6-months-old male and female zebrafish Swiss male albino mice (20-25 g)	225 mg/kg for fish 100mg/kg for mice	onset of cyclonic seizure and clonic seizure death	[37]
Azima tetracantha	Ethanol/ root	250 and 500 mg/kg	adult male mice	80 mg/kg	onset of clonic phase, Death	[38]
Murraya koenigii	Aqueous/ leaf	200 and 300 mg/kg	Swiss albino mice of either sex	50 mg/Kg	clonic convulsion	[39]
Acorus calamus	Ethanol/ Rhizome	250 mg/kg 500mg/kg	male Swiss albino mice weighing 25-30g	80 mg/kg *s.c*	myoclonic jerks, clonic seizures or death	[40]

CONCLUSION

PTZ induced animal model is one of the commonly used animal models for biological screening of antiepileptic drugs. This review discussed in detail about PTZ animal model in preclinical research and future this review is useful for the researchers to study the antiepileptic activity.

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Nil

CONFLICT OF INTEREST

Nil

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