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PHARMACOLOGICAL COMPARISON OF ANTI-EPILEPTIC ACTIVITIES OF POLYHERBAL FORMULATIONS EPIFIX CAPSULE, EPIDIOLEX ORAL SOLUTION AND SARASWATARISHTHA SYRUP

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ABSTRACT

The purpose of this pharmacological study was to assess the anti-epileptic properties of polyherbal formulations such as Saraswatarishtha Syrup (Baidyanath) (BSS), Epidiolex Oral Solution (Jazz Pharmaceuticals) (JPEOS), and Epifix Capsule (Matsyaveda) (MEC) in rats. JPEOS has one SPM from one medicinal herb, BSS has 230 SPMs from twenty-three medicinal herbs, and Polyherbal Formulations MEC has over 88 SPMs and pharmacotherapeutics from nine medicinal plants and herbs. Additionally, the polyherbal formulations BSS, MEC, and JPEOS had significant TPC content, and the antioxidant potential of each formulation was closely correlated with their TPC concentration. The BSS had a comparatively higher TFC content than MEC and JPEOS. Significant antioxidant activity was seen when the reducing power of the BSS, MEC, and JPEOS formulations increased with dosage. BSS has a reasonably large safety margin and is classified as non-toxic. Animals were pretreated with ployherbal formulations BSS, MEC, and JPEOS for fifteen days before seizures were produced using the MES method, according to *in-vivo* anti-epileptic action. BSS proved effective in treating epileptic seizures; for example, pre-treatment with BSS formulation dramatically reduced the duration of convulsions and shortened the flexion phase of MES-induced seizures. It was discovered that the ployherbal formulations BSS and MEC were less effective than the common drug Phenytoin, but more effective than lesser dosages. Additionally, both BSS and MEC improved the anti-epileptic

effects and reduced the convulsion phase. Comparatively speaking, JPEOS was less successful than BSS and MEC.

KEYWORDS: Anti-epileptic, antioxidant, epileptic seizures, ployherbal formulations, safety margin, total phenolic content, total flavonoid content.

INTRODUCTION

According to Paul *et al*., 2009, epilepsy is characterised by a high frequency of abrupt, excessive discharges in cerebral cortical neurones, which can cause disruptions in consciousness, sensation, mental function, and movement, or a combination of these symptoms. According to Deshmukh and Thakur (2011), strong, poorly synchronised, restricted, or widely distributed electrical discharges from neurones cause epilepsy, a brain condition (Fig.1). The disorder results from abnormal brain activity caused by a genetic condition, head trauma, brain diseases, or developmental issues. An epileptic seizure is a period of aberrant neuronal discharge that manifests clinically as altered sensory perception, motor coordination, mood, or autonomic function.

According to WHO (2005), trauma, status epilepticus (12.5% of all epilepsy deaths), and sudden unexpected death (2–18%) are all directly linked to an elevated risk of dying from epilepsy. According to the WHO (2016), epilepsy is the most severe chronic illness of the central nervous system, affecting around 50 million individuals worldwide. Its prevalence rate is approximately 10 per 1000 people, and its incidence rate is between 30 and 60 per 100,000 people annually.

According to Newton and Garcia (2012), 70 million individuals globally are thought to have epilepsy, with over 85% of cases occurring in low-income and lower middle-income (Fig.2). Epilepsy is highly prevalent among persons of all ages. Based on their clinical manifestation, a wide variety of seizure types can be distinguished (Marjan *et al*., 2011).

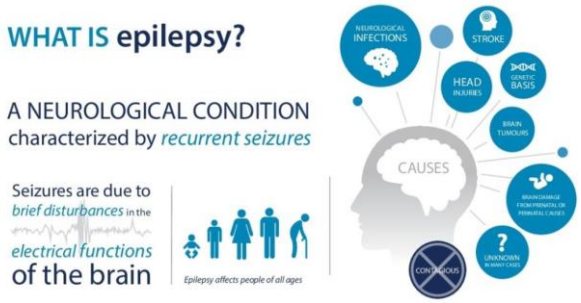

Fig. 1: Epilepsy - common chronic neurological disorder.

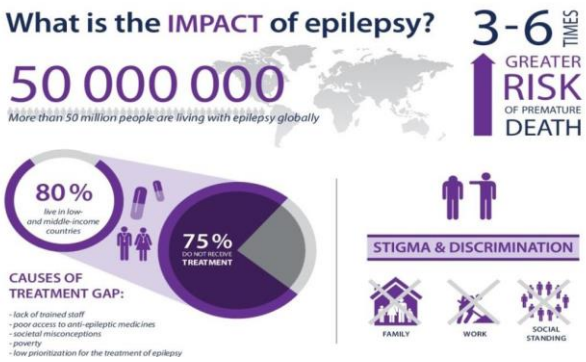

Fig. 2: Impact of Epilepsy.

Classification of Epilepsy

Sharma (2007), classification based on seizure types and their characteristic symptoms of seizures: Epilepsy can be broadly categorized into generalised and partial (Localised) epilepsy type. Generalized seizures include larger areas on both sides of the brain and loss of consciousness while a partial seizure initiates in a small area on one side of the brain and induces milder symptoms.

I. Generalised Seizure

(i). Grand mal or tonic-clonic seizures

(ii). Petit mal or Simple absence seizures

(iii). Myoclonic seizures

(iv). Akinetic (Atonic) seizures

(v). Clonic seizures

(vi). Tonic seizures

II. Partial Seizures (Localised/ Focal)

(i) Simple partial seizure

(ii) Complex partial seizure

III. Unclassified seizures

(i) Febrile seizures

(ii) Infantile spasm

Etiology, Pathophysiology and Prognosis of Epilepsy

Epilepsy has several causes which are presented below

1. Genetic or hereditary: epilepsies such as juvenile myoclonic, childhood absence epilepsy

syndrome.

2. Brain damage mainly during birth

3. CNS infections like cerebral meningitis and brain abscess

4. Metabolic disorders like lack of oxygen, alkalosis, hypoglycemia, hypocalcemia, hyperpyrexia, uremia, hypoxia and vit. B6 deficiency.

5. Cerebrovascular vascular diseases hemorrhage, hypotension.

6. Benign Febrile convulsion associated with fever in children under the age of two.

7. Sudden withdrawal of many drugs of abuse such as barbiturates and alcohol.

Pathophysiology of Epilepsy

Synchronous neuronal discharges within a specific set of neurones, which are commonly reported in the cerebral cortex but can be seen in other parts of the brain, are what cause epileptic seizures. Aberrant motions, sensations, or ideas are caused by aberrant discharges that are initiated and spread to other areas of the brain. Although the exact neuronal mechanisms causing a seizure are yet unknown, there is growing evidence that glutamate-mediated increased excitatory neurotransmission plays a role (Fig.3). Researchers think that too much glutamate activates NMDA receptors, which moves Mg+2 out of the NMDA-calcium ionophore and makes it easier for calcium to enter neurones. By stimulating the production of nitric oxide, calcium is believed to play a role in the long-term enhancement of excitatory glutamate neurotransmission.

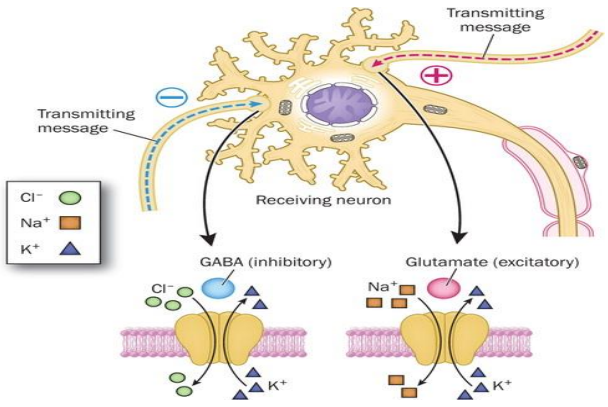

Fig. 3: Pathophysiology of Epilepsy.

Kasper *et al*., 2015, after diffusing to the presynaptic neurone, nitric oxide increases the release of glutamate by forming cyclic guanosine monophosphate**.** These activities increase calcium influx and NMDA receptor activation, which are thought to be involved in the depolarisation shift seen in seizure foci. Long-term potentiation is caused by increased

excitatory glutamate neurotransmission. A depolarisation shift characterised by protracted depolarisations with spikelets is thought to be facilitated by long-term potentiation. Adjacent neurones may release simultaneously as a result of the depolarisation shift, which could cause a seizure.

Treatment of Epilepsy

McNamara (1996), drugs aim to control and prevent all seizure activity at an acceptable level of side effects. Some general principles of symptomatic treatment with antiepileptic drugs are (Fig.4)

a. The choice of drugs and dose is according to the seizure type and needs of the individual patient. Major standard of anticonvulsant drugs is Phenytoin, Carbamazepine, and Valproate.

b. Treatment starts with a single drug, initial low dose gradually increases till full control of seizure or up to the appearance of side effects. Unless full control is obtained at a maximum tolerated dose of one drug, attempt another drug as a substitute. Use polytherapy when all possible monotherapy fails.

c. Gradually stop the therapy otherwise sudden withdrawal of therapy causes status epilepticus.

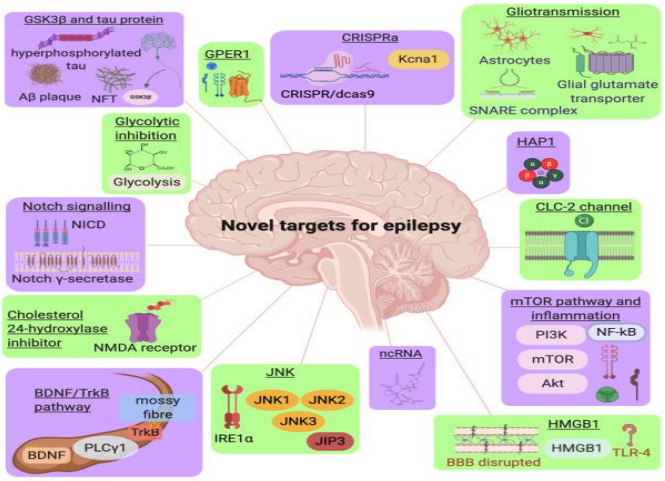

Fig. 4: Novel targets for Epilepsy.

Mechanism of Action of Anti-epileptic Drugs (Fig.5)

Seizures occur whenever there is an imbalance or defects in

a. Neuronal membrane conductance of Na+ or Ca2+ ions
b. Defects in GABA transmission caused by inhibitory GABA neural circuits
c. NMDA receptor channel-based excitatory method to cause depolarisation
d. Additional pre- or postsynaptic activity-related tasks.

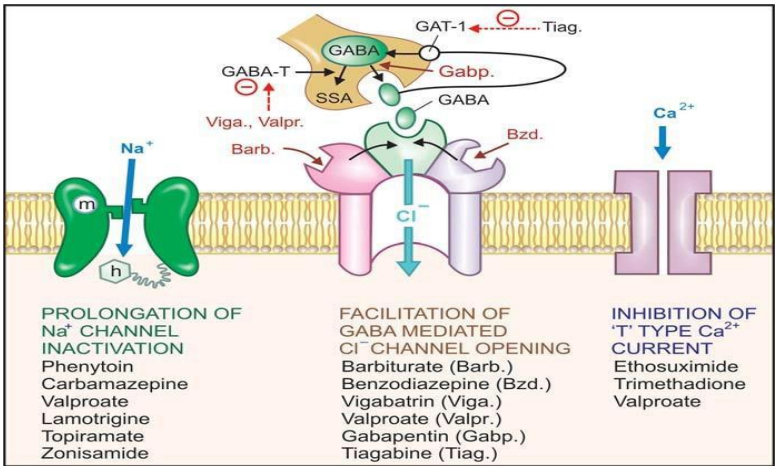

Fig.5: Major mechanisms of anti-convulsant actions m: Activation gate; h: Inactivation gate; GABA-T: GABA transaminase; SSA: Succinic semialdehyde; GAT-1: GABA transporter (Tripathi, 2006).

As a result, anticonvulsant drugs can act by different mechanisms to suppress repetitive firing action potentials by an epileptic focus in the brain.

Allopathic Medicine

According to Yasuyo *et al*., 2006, there are a lot of allopathic medications available to treat epilepsy, however they all have a lot of negative effects. Because plant sources have relatively little adverse effects, they could be a good alternative for treating epilepsy. There are very few herbal formulations available on the market to treat epilepsy (Olufunmilayo *et al*., 2007). According to Zaccara et al., 2014, up to 81.3% of patients using antiepileptic medication (AED) such as carbamazepine, valproate, and lamotrigine experienced adverse drug reactions (ADRs) (Dalic and Cook, 2016). In over 70% of cases, current antiepileptic medications are successful in treating seizures; nevertheless, their usage is frequently restricted due to adverse effects (Perucca and Gilliam, 2012).

Alternative Therapy of Epilepsy

Severe side effects, addiction liabilities and continue therapeutic drug monitoring during therapy associated with widely prescribed antiepileptic synthetic drugs indicates the need for new drugs as an alternative. Alternative therapies include Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy (AYUSH).

In Ayurveda, the ancient period of time medicinal plants frequently used as antiepileptic whose effect confirmed worldwide which comprises, Brahmi (Indian pennywort) *Bacopa*

monnieri, shatawary (*Asparagus racemosus*), Vacha (sweet flag) *Acorus calamus*, Kushtha (*Saussurea lappa*), Shankhpushpi (*Convolvulus pluricaulis*), mulethi (*Glycyrrhiza glabra*), agastya leaves (*Sesbania grandiflora*), garlic, ginger, zing (Asafoetida), pumpkin, *uncarya rhyncophylla, gastrodia ellata*.

Sarmaukaddam *et al*., 2010, herbal therapy can make epilepsy treatment more rationale and patients friendly because of its fewer side effects and interactions (Bhargava and Khan, 2012). Many plants have been reported to possess antiepileptic activity by preclinical studies. Accordingly, considering the need for medicinal plants as an alternative to modern medicines in epilepsy management traditionally claimed *A. lebbeck, M. longifolia, A. heterophyllus and I. reniformis* plants were selected for the present investigation.

Schematic Antiepileptic Study of Herbal Drugs

The perfect antiepileptic medication will purposefully suppress every seizure without causing any adverse effects. Unfortunately, the medications currently in use frequently cause negative effects in addition to failing to control seizure activity in some patients. According to Lee *et al*., 2005, there are various allopathic medications that can be used to treat epilepsy, but they all have a lot of negative side effects. Due to their lack of adverse effects, plant sources could be a good alternative for treating epilepsy. There are very few herbal remedies available to treat epilepsy. The plant Ananas camosus raises serotonin levels in the brain, which helps GABA attach to its receptors.

Matsyaveda Epifix capsules, an Ayurvedic supplement for neurological support, contain a blend of herbs like Ashwagandha**,** Brahmi**,** Shankhpushpi**,** Jatamansi**,** Vacha**,** Mandukaparni, plus minerals like Bhasmas (Ash, Silver, Pearl)**,** aimed at calming the nervous system, reducing seizure frequency, and improving brain function, though specific ingredient quantities often vary and are best confirmed on the product label or official site.

Key ingredients often found in Epifix capsule

Herbal Extracts: Ashwagandha, Brahmi (*Bacopa monnieri*), Shankhpushpi (*Convolvulus pluricaulis*), Jatamansi (*Nardostachys jatamansi*), Vacha (*Acorus calamus*), Mandukaparni (*Centella asiatica*).

Minerals/Bhasmas: Ash Bhasma (Calcined Ash), Rajat Bhasma (Silver Ash), Mukta Bhasma (Pearl Ash).

The Epidiolex (cannabidiol) oral solution manufactured by Jazz Pharmaceuticals contains cannabidiol as the active ingredient, alongside specific inactive ingredients. Cannabidiol (CBD): Each milliliter (mL) of the oral solution contains 100 mg of highly purified cannabidiol, derived from the *Cannabis sativa* L. plant. It does not contain THC (tetrahydrocannabinol), the compound associated with a "high".

The name Saraswatarishta The 18 herbal ingredients in Saraswatarishtam, a potent nervine tonic, are all intended to treat and manage a variety of neurodegenerative disorders, including vertigo, ADHD, heart disease, depression, slurred speech, fatigue, low grasping power, acute anxiety, depression, and loss of appetite. Neurological disorders such as Parkinson's disease, which affects movement, Alzheimer's disease, which affects memory and abilities, dementia, which affects thinking and memory, which causes tremors can also be treated. Baidyanath Saraswatarishta Syrup is an ayurvedic memory tonic that raises immunity, boosts strength, and calms the nervous system. It can be used to treat convulsions, memory loss, stammering, nerve debility, and seminal weakness. There is 5-10% self-generated alcohol in Saraswatarishta. Baidyanath Saraswatarishta Liquid is used to help detoxification, improve the immune system, ease stomach discomfort, and maintain healthy brain function. Brahmi, Haritaki, Ashwagandha, Guduchi, and other traditional Ayurvedic herbs are blended into its formulation.

Review of Screening Models used for the Study

The literature survey concluded as seizures can be induced in animals by a wide range of screening methods mainly electrical or chemical stimulation. MES, PTZ and other chemoconvulsant and kindling models are the most common methods were used for evaluating the antiepileptic drugs in preclinical studies. Preclinical antiepileptic screening of herbal plants gives support to the traditional claim of herbal anti-epileptics.

Maximal Electric Shock Method

Merritt and Putnam adapted MES simple and consistent model in 1930 for the discovery of phenytoin. Maximal Electroshock Seizure (MES) model is one of the ideal models in the early stage of AEDs screening. The MES induced convulsions in animals depict grand mal type of epilepsy in man. In the MES test, rats or mice get an electrical stimulus 50-mA 0.2-s (mice) or 150-mA 0.6-s (rats) to persuade maximal seizures of their hind limbs, with tonic extension as the endpoint of the test. The maximal electroshock test is to evaluate the capability of an anticonvulsant drug to diminish the tonic, hind limb extension.

PTZ Induced Seizures

In the late 1800s researchers started to induce seizures in animals using PTZ for the AEDs screening. Richard and Everett used the PTZ seizure model in mice for the investigation of trimethadione in 1944. PTZ is a CNS stimulant. PTZ a tetrazole derivative is the prototype agent in the case of systemic convulsants. PTZ has been described to act through the GABA-benzodiazepine receptor mechanism in the brain. (Swinyard et al., 1952).

Wistar albino rats were used in this study to induce seizures using the maximal electroshock method (MES). The anti-epileptic properties of polyherbal formulations such as Saraswatarishtha Syrup (Baidyanath), Epidiolex Oral Solution (Jazz Pharmaceuticals), and Epifix Capsule (Matsyaveda) were investigated with the following goals and objectives

- Using contemporary scientific methods of phytochemical screening, the polyherbal compositions Epifix Capsule, Epidiolex Oral Solution, and Saraswatarishtha Syrup are qualitatively analysed.
- To investigate the brain-boosting activity of polyherbal formulations such as Saraswatarishtha Syrup, Epidiolex Oral Solution, and Epifix Capsules in vitro.
- To conduct comparative pharmacological studies in vivo for anti-epileptic purposes using polyherbal formulations such as Saraswatarishtha Syrup, Epidiolex Oral Solution, and Epifix Capsule.
- To determine the pharmacodynamics of different actions.

MATERIALS AND METHODS

Collection of Materials, Chemicals and Drugs

Polyherbal Formulations Epifix Capsule, Epidiolex Oral Solution and Saraswatarishtha Syrup were procured from concerned companies and reliable commercial source and analytical grade chemicals and reagents were used in the different studies.

Pharmacognostical and Pharmacological Assessment

Composition of Polyherbal Formulations Epifix Capsule (Matsyaveda)

Table 1: Composition of Epifix Capsule (Matsyaveda).

Scientific Name, Family with Vernacular Name and Part used)	Quantity(mg)
Bauhinia variegata (Fabaceae) Kachnar (leaves)	10
Withania somnifera (Solanaceae), Ashwagandha (Fruits)	10
Celastrus paniculatus (Celastraceae), Malkangni (Seed)	10
Acorus calamus (Acoraceae), Bach / Vach (rhizome / root)	5
Rauwlolfia serpentina (Apocyanaceae), Sarpagandha (root)	5

Delphinium denudatum (Ranunculaceae), Nirbishi (root)	10
Paeonia emodi (Paeoniaceae), Chandra / Udsalap (root)	10
Pimpinella anisum (Apiaceae), Choti Saunf (fruit/seed)	5
Convolvulus pluricaulis (Convolvulaceae), Shankhpushpi (whole plant)	10
Total	75

Composition of Polyherbal Formulations Epidiolex Oral Solution

Table 2: Constituents of 1 ml of Epidiolex oral solution (Jazz Pharmaceuticals).

Scientific Name, Family, Vernacular Name and Part used	Quantity (mg/ml)
Cannabis sativa L. (Ganja / bhang / marijuana (flowers / buds; Cannabaceae ; Cannabidiol Oral solution / CBD)	100

Polyherbal Saraswatarishtha Syrup Composition

Table 3: Composition of Each 10 ml of Baidyanath Saraswatarishtha Syrup.

S. No.	Scientific Name, Vernacular Hindi Name and Family	Quantity(mg)
1.	*Bacopa monnieri* / Brahmi	2.188
2.	*Asparagus racemosus* / Satavari (Asparagaceae)	546.666
3.	*Pueraria tuberose* / Vidari (Fabaceae)	546.666
4.	*Terminalia chebula* / Haritaki (Combretaceae)	546.666
5.	*Chrysopogon zizanioides* / Usira (Poaceae)	546.666
6.	*Zingiber officinale* / Sunthi (Zingiberaceae)	546.666
7.	*Foeniculum vulgare* / Misreya (Apiaceae)	546.666
8.	*Glycyrrhiza glabra* / Madhu (Fabaceae)	1094.00
9.	*Saccharum officinarum* / Sarkara (Poaceae)	2733.00
10.	*Woodfordia fruticosa* / Dhataki (Lythraceae)	546.666
11.	*Vitex agnus-castus* / Renuka (Lamiaceae)	27.333
12.	*Operculina turpethum* / Trivrt (Convolvulaceae)	27.333
13.	*Piper longum* / Pippali (Piperaceae)	27.333
14.	*Syzygium aromaticum* / Lavang (Myrtaceae)	27.333
15.	*Acorus calamus* / Vaca (Acoraceae)	27.333
16.	*Saussurea lappa* / Kushtha (Asteraceae)	27.333
17.	*Withania somnifera* / Ashwagandha (Solanaceae)	27.333
18.	*Terminalia bellirica* / Bibhitaki (Combretaceae)	27.333
19.	*Tinospora cordifolia*/ Guduchi (Menispermaceae)	27.333
20.	*Elettaria cardamomum* / Ela (Zingiberaceae)	27.333
21.	*Embelia ribes* / Vidanga (Primulaceae)	27.333
22.	*Cinnamomum zeylanicum* / Tvak (Lauraceae)	27.333
23.	*Cassia angustifolia* / Swarnapatri (Leguminaceae)	27.333
	Grand Total	8011.179
	Asav Base	Q.S.

Qualitative Chemical Test Analysis

Using conventional protocols outlined by Trease & Evans (1985), Sofowora (1993), Khandelwal (2008), Harborne (1973), and Kokate (2005), MEC, JPEOS, and BSS were

employed for phytochemical experiments.

Estimation of TPC in MEC, JPEOS and BSS

The spectrophotometric analytical method of Jeong *et al*., 2010, was used in this work to try and determine the TPC in MEC (Matsyaveda), JPEOS (Jazz Pharmaceuticals), and BSS (Baidyanath).

Estimation of Total Flavonoid Content (TFC)

According to Negro *et al*., 2003, the calibration curve was prepared using the TFC estimation method using quarcetin as the standard. The colorimetric assay was used in this investigation to determine the TFC of MEC, JPEOS, and BSS (Kamtekar *et al*., 2014). Standard quercetin solutions at concentrations of 100, 200, 400, 600, 800, and 1000 µg/ml were made in 1 millilitre. The standard samples' absorbance was measured at 510 nm. TFC is measured in milligrammes of quercetin equivalent per 100 mg of extract. TFC in MEC, JPEOS and BSS were examined and computed, and a standard plot was created (Fig.6).

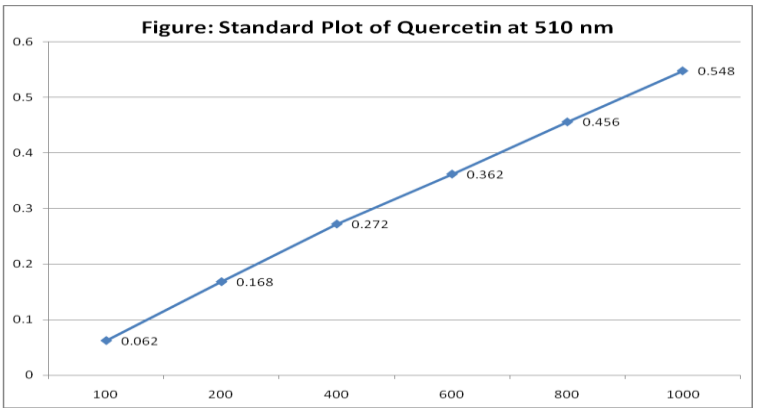

Fig. 6: Quercetin calibration (510 nm).

Table 4: TFC in polyherbal formulations BSS, MEC, and JPEOS.

Formu -lation	UV Absorbance	TFC Conc. Eq. to Quercetin (µg/1 ml)	TFC (quercetin mg equivalent/100 mg of extract)
MEC	0.484	786	7.8
JPEOS	0.372	614	6.1
BSS	0.588	990	9.9

***In-vitro* Antioxidant Activity**

Gutteridgde, 1995 reported that various diseases are caused due to free radicals induced oxidative stress (Osawa *et al*., 1990; Marletta *et al*., 1989). *In-vitro* antioxidant activity of

polyherbal Formulations Epifix Capsule (MEC), Epidiolex Oral Solution (JPEOS) and Saraswatarishtha Syrup (BSS) by DPPH scavenging activity and FRAP Assay.

DPPH Free Radical-Scavenging Activity

The BSS, MEC, and JPEOS ability to scavenge free radicals was determined using Krings & Berger's (2001) approach. As a standard and blank free radical scavenger, 50% methanol was utilised, while trolox served as a positive control. 600 µl of DPPH was added after varying the concentrations (30-300 µg/ml) using the stock of each sample (3 mg/ml). Following a 20-minute incubation period, the absorbance at 517 nm was determined for the reaction mixture. (Yen and Duh, 1994)

Ferric Reducing / Antioxidant Power (FRAP) Assay

The FRAP of BSS, MEC, and JPEOS was calculated using Benzie & Strain's (1996) methodology. These quantities were then combined with 1 millilitre of FRAP reagent, and the mixture was incubated for 30 minutes in the dark. To keep track of the sample's capacity to convert ferric ions into ferrous ones, the absorbance of the reaction mixture was measured at 593 nm (Fig.7-8).

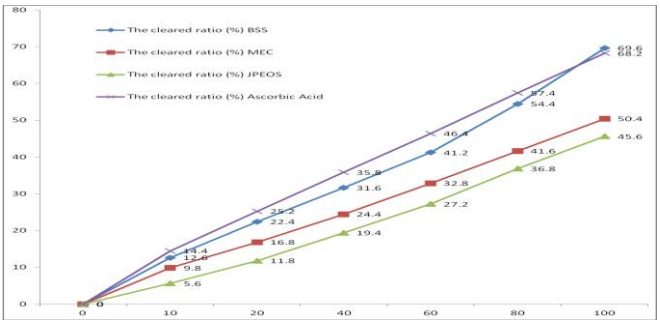

Fig. 7: The regression curve of DPPH.

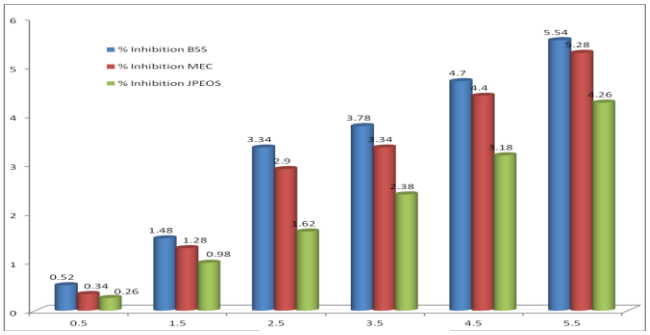

Fig. 8: Effect of BSS, MEC, JPEOS on FRAP Assay.

Safety & Toxicity Evaluation

BSS, MEC, and JPEOS extracts were administered and physiological and behavioral changes

were analysed (Fig. 9-14).

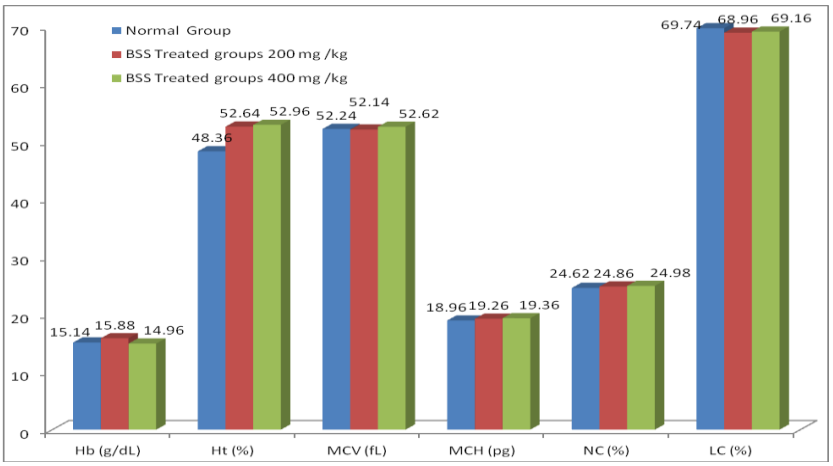

Fig. 9: BSS effects on blood analysis tools.

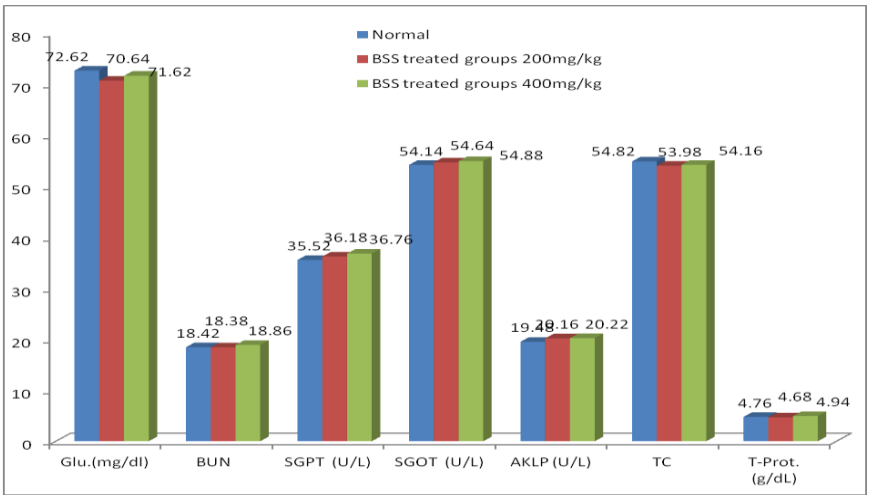

Fig. 10: HSS effect on LFTs and blood values.

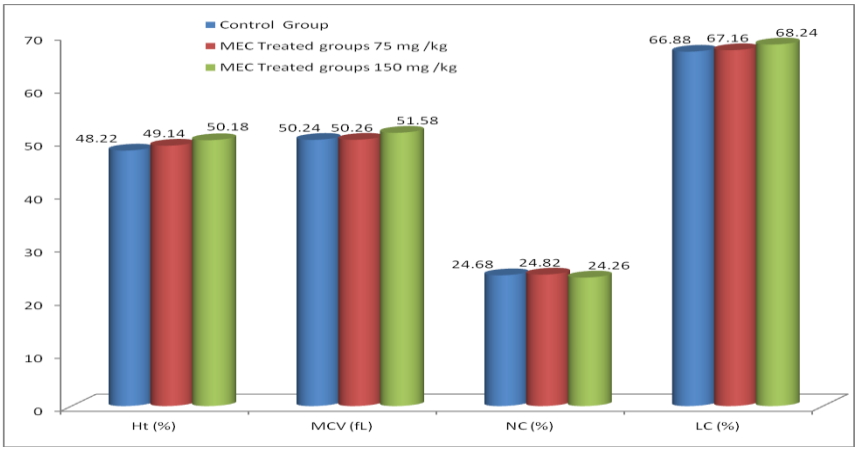

Fig. 11: MEC effects on different blood values.

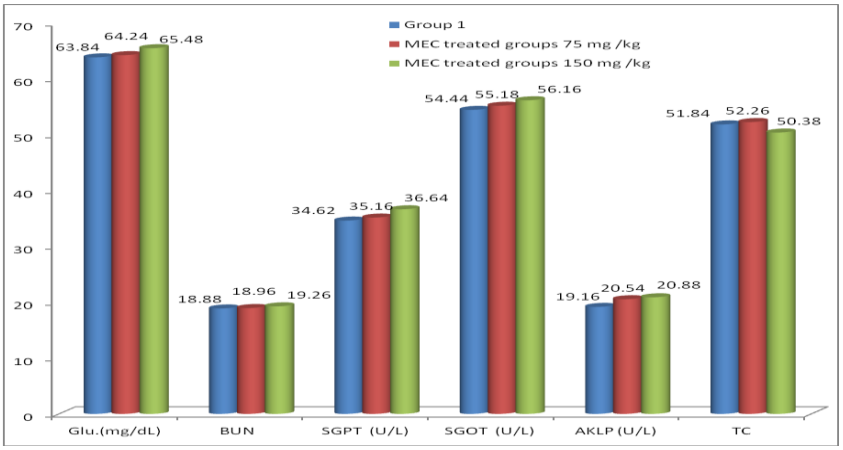

Fig. 12: MEC effects on blood quality.

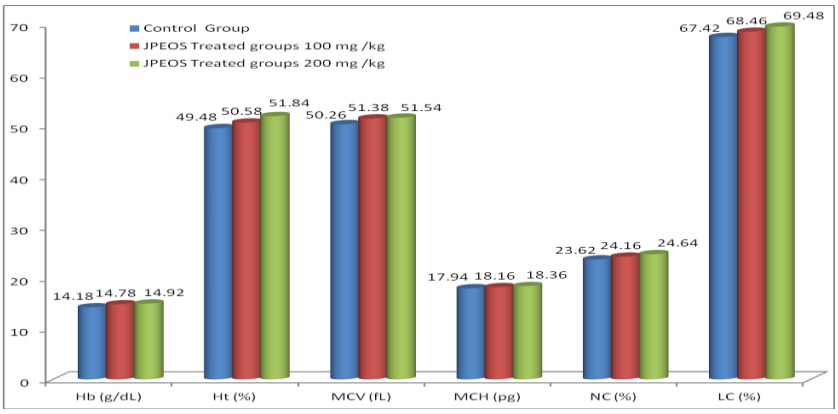

Fig. 13: JPEOS effects on different blood values.

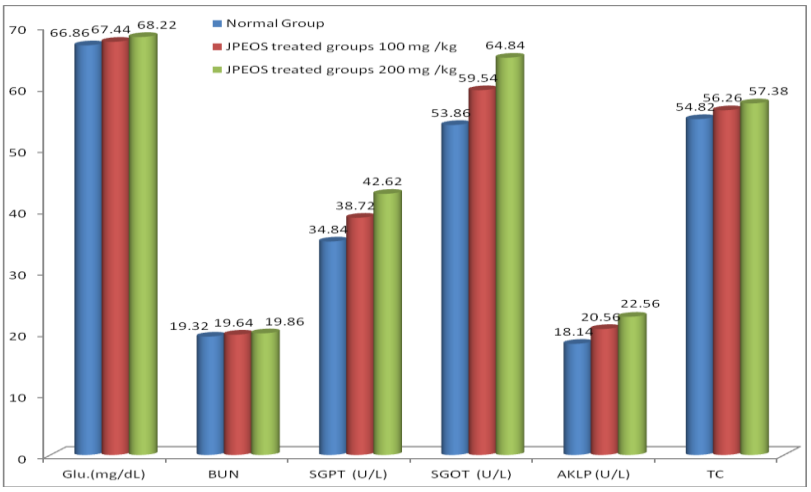

Fig. 14: JPEOS effects on blood quality.

In-vivo anti-epileptic activity

IAEC Form B for approval of Animal study: IEC/IAEC/2026/03 dated 20-2-26. Loscher and Schmidt 2011, derived MES Induced Seizures model used (Table 5; Fig. 15-17).

Table 5: BSS, MEC and JPEOS effects on MES-induced seizures.

Groups	Flexion (sec)	Extension (sec)	Convulsion (sec)	Recovery time (min)	% protection
Group I	---	---	---	---	---
Group II	5.44 ± 0.32	8.86 ± 0.34	25.84 ± 4.44	4.18 ± 0.22	--
Group III	2.84± 0.22***	6.78 ± 0.42*	16.66 ± 3.16	2.44 ± 0.14*	77.46
Group IV	3.24± 0.24**	7.26 ± 0.32	17.16±3.26*	2.86 ± 0.22	64.22
Group V	3.48 ± 0.12*	8.48 ± 0.54	22.16 ± 3.72	3.28 ± 0.16	54.62
Group VI	1.36 ±0.06***	1.64±0.54***	14.82±1.28*	1.14±0.06***	84.24

Nate: values: Mean ± SE (***$P < 0.001$; *$P < 0.05$).

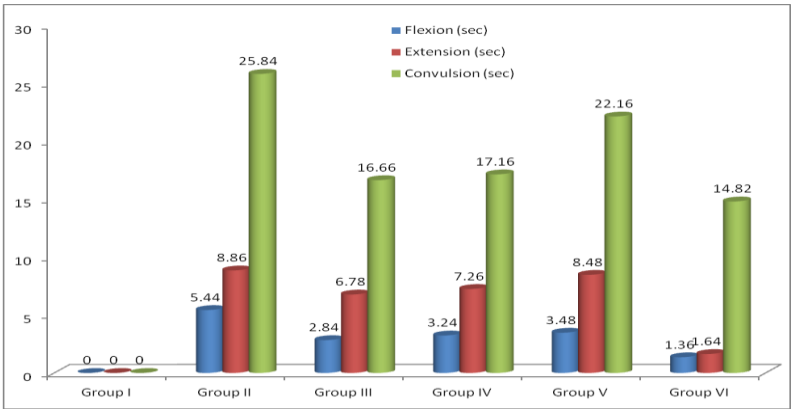

Fig. 15: Impact on seizures.

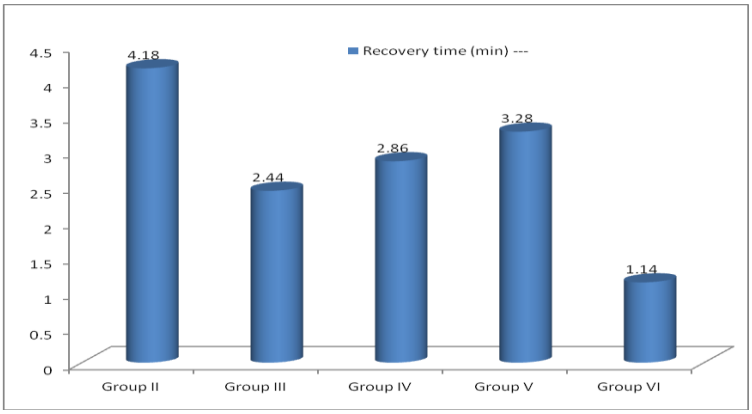

Fig. 16: Recovery time (min) in seizures.

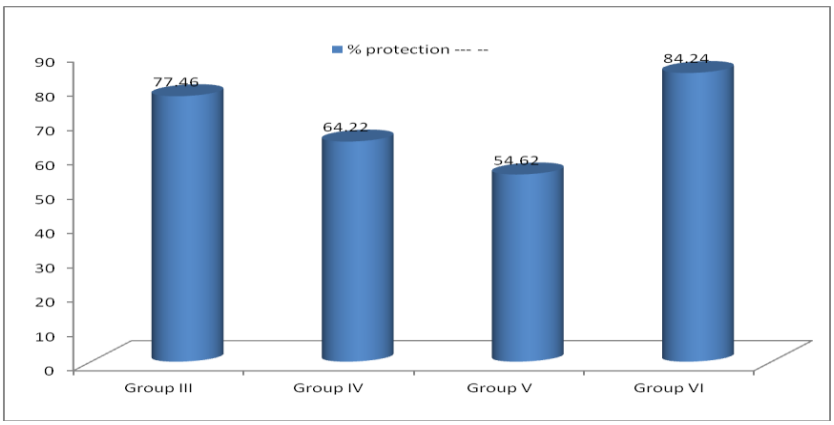

Fig. 17: % protection in seizures.

RESULTS AND DISCUSSION

Epifix Capsule (Matsyaveda) contains dried extract of 09 medicinal plants which include *Bauhinia variegata* (Kachnar leaves; Fabaceae), *Withania somnifera* (Ashwagandha Fruits; Solanaceae;), *Celastrus paniculatus* (Malkangni Seed; Celastraceae), *Acorus calamus* (Bach / Vach rhizome / root; Acoraceae), *Rauwlolfia serpentine* (Sarpagandha / Nakulikand root; Apocyanaceae), *Delphinium denudatum* (Nirbishi root; Ranunculaceae), *Paeonia emodi* (Chandra / Udsalap root; Paeoniaceae), *Pimpinella anisum* (Choti / Saunf fruit/seed; Apiaceae), and *Convolvulus pluricaulis* (Shankhpushpi whole plant; Convolvulaceae) with more than eighty eight (88) SPMs.

The polyherbal Baidyanath Saraswatarishtha Syrup (BSS) formulation contains extracts of 23 medicinal plants like *Bacopa monnieri* / Brahmi, *Asparagus racemosus* / Satavari (Asparagaceae), *Pueraria tuberose* / Vidari (Fabaceae), *Terminalia chebula* / Haritaki (Combretaceae), *Chrysopogon zizanioides* / Usira (Poaceae), *Zingiber officinale* / Sunthi (Zingiberaceae), *Foeniculum vulgare* / Misreya (Apiaceae), *Glycyrrhiza glabra* / Madhu (Fabaceae), *Saccharum officinarum* / Sarkara (Poaceae), *Woodfordia fruticosa* (Lythraceae), *Vitex agnus-castus* / Renuka (Lamiaceae), *Operculina turpethum* / Trivrt (Convolvulaceae), *Piper longum* / Pippali (Piperaceae), *Syzygium aromaticum* / Lavang (Myrtaceae), *Acorus calamus* / Vaca (Acoraceae), *Saussurea lappa* / Kushtha (Asteraceae), *Withania somnifera* / Ashwagandha (Solanaceae), *Terminalia bellirica* / Bibhitaki (Combretaceae), *Tinospora cordifolia*/ Guduchi (Menispermaceae), *Elettaria cardamomum* / Ela (Zingiberaceae), *Embelia ribes* / Vidanga (Primulaceae), *Cinnamomum zeylanicum* / Tvak (Lauraceae), *Cassia angustifolia* / Swarnapatri (Leguminaceae) as ingredients with more than 230 SPMs.

Polyherbal Formulations Matsyaveda Epifix Capsule (MEC) contains more than 88 SPMs / pharmacotherapeutics from 09 Medicinal Plants / Herbs, Jazz Pharmaceuticals Epidiolex Oral Solution (JPEOS) contains 01 SPM from 01 Medicinal Plants / Herbs and Baidyanath Saraswatarishtha Syrup (BSS) contains 230 SPMs from 23 Medicinal Plants / Herbs**.** Matsyaveda Epifix Capsule (MEC) is useful for ADHD, Jazz Pharmaceuticals Epidiolex Oral Solution (JPEOS) is used for Mental agitation, anxiety, sadness, migraines, mental exhaustion, memory loss and Baidyanath Saraswatarishtha Syrup (BSS) violent mental agitation. On the basis of comparison of composition, dose and toxicity profile BSS was found to be better then MEC and JPEOS.

Phytochemical screening / analysis of MEC, JPEOS and BSS showed the presence of

alkaloids, glycosides, tannins, flavonoids, terpenes, phenolics, proteins, amino acids etc as summarized. The amount of the TPC in the MEC, JPEOS and BSS were found to be 9284.26±4.52 (mg GAE/100 gDW), 718.12±3.86 (mg GAE/100 gDW) and 1296.44±4.82 mg GAE/100 gDW and respectively. TPC levels were high in the MEC and BSS (antioxidant activity is directly related to TPC levels).

TFC is measured in milligrammes of quercetin equivalent per 100 mg of extract. TFC in MEC, JPEOS and BSS were examined and computed, and a standard plot was created. Comparatively high amount of TFC was found in the BSS/Saraswatarishtha Syrup (9.9 mg of Quercetin eq./100 mg crude extract) and more than MEC/ Epifix Capsule (7.8 mg of quercetin equivalent/100 mg crude extract) and JPEOS / Epidiolex Oral Solution (6.1mg of quercetin equivalent/100 mg crude extract).

BSS showed a percentage inhibition in the DPPH assay between 12 and 62%, whereas MEC extract showed a percentage inhibition between 9 and 50% and JPEOS extract showed a percentage inhibition between 5 and 45%. BSS extract had an IC50 value of 11.42, whereas MEC had an IC50 value of 18.42 and JPEOS an IC50 value of 24.82 (lower IC50 values indicate better antioxidant activity).

Toxicity assessment of polyherbal BSS, MEC, and JPEOS formulations in wistar rats as per OECD-423 guidelines. There was no hazardous or harmful effect from acute oral toxicity up to 2000 mg/kg p.o. dose, suggesting that formulation BSS and MEC are safe to use at high dosages. Studies on BSS and MEC acute toxicity revealed no death in rats at doses up to 2000 mg/kg/b.wt. BSS and MEC categorized as non-toxic (fairly wide safety margin). Formulation BSS and MEC formulations were administered no destructive physiological and behavioral alterations whereas JPEOS induced severe toxicities.

Acute toxicity experiments in BSS and MEC showed no mortality. In JPEOS, atherosclerosis, decreased engine function, and other behavioural abnormalities were observed. No disruptions / alteration in KFTs, LFTs, and haematological markers were observed. BSS and MEC possess very high safety margin (classified as non-toxic constituents). Acute toxicity experiments in JPEOS showed severe toxicities. Aniamls in Group I (Normal Control) had unlimited access to water. Group II (Toxic Control group): The maximum electroshock method (MES) was used in this study to produce seizures in wistar albino rats. Group III: Saraswatarishtha Syrup (400 mg/kg) plus electroshock for seven days, followed by MES-

induced seizures. Group IV (Epifix Capsule + Electroshock): Albino rats in Group IV received a pre-treatment of 75 mg/kg of Epifix Capsule before seizures were generated using the MES method. Group V (Epidiolex Oral Solution + Electroshock): rats were treated with 100 mg/kg of Epidiolex Oral Solution, and then MES was used to induce seizures. Phenytoin sodium (Standard) was administered at a dose of 25 mg/kg in Group VI (Standard drug: Phenytoin + Electroshock). Phenytoin, a common medication, was administered to Group VI animals before MES was used to induce seizures. Similar to the usual medication Phenytoin/Saraswat Syrup, MEC was dose-dependent anticonvulsant effects were produced by pretreatment with BSS and MEC extracts.

After fifteen days of pre-treatment with ployherbal formulations BSS, MEC, and JPEOS, the MES method was used to produce seizures in the animals. Animals in Group VI (Standard drug: Phenytoin (25 mg/kg) + Electroshock) received phenytoin for 15 days before MES was used to induce seizures. Lastly, animals in Group III BSS (400 mg/kg p.o.) + Electroshock were treated with Baidyanath Saraswatarishtha Syrup for 15 days before MES was used to induce seizures. In epileptic seizures, 400 mg/kg BSS was efficacious ($P<0.05$). For example, pre-treatment with 400 mg/kg BSS formulation dramatically reduced the duration of convulsions (***$P<0.001$) and shortened the flexion phase of MES-induced seizures. Lastly, the albino rats were deemed protected if they stopped tonic hind limb extension within 10 seconds of the electroshock being administered. Groups III, IV, and V had dose-dependent anti-epileptic effects after pre-treatment with ployherbal formulations BSS, MEC and JPEOS. Ployherbal formulations BSS and MEC were found to be more effective than lower dosages but less effective than the usual medication Phenytoin. Pre-treatment with BSS (Group III) and MEC (Group IV) dramatically reduced the duration of convulsions (***$P<0.001$) and may have reduced the flexion phase of MES-induced seizures. Additionally, both BSS and MEC produced superior anti-epileptic effects and reduced the convulsion phase.

Further, it showed a significant decrease in the recovery time (righting reflex), demonstrated that formulation BSS and MEC in reducing seizures caused by MES. The substantial protection provided against MES-induced seizures may be the reason why it was not surprising that the formulation BSS and MEC markedly raised in brain.

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