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Research Article

Exploring the Anticonvulsant Activity of Aqueous Extracts of *Ficus benjamina* L. Figs in Experimentally Induced Convulsions

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Background. *Ficus benjamina* L. is an evergreen tree, native to Southeast Asia, and often known as a weeping fig. Its latex and fruit extracts are used by indigenous cultures to cure skin conditions, inflammation, vomiting, leprosy, malaria, and nasal ailments. The aqueous extract of the figs of *Ficus benjamina* L. has various therapeutic values, including biological activities on the central nervous system. *Materials and Methods*. The extract of the dried figs of *Ficus benjamina* L. (FBE) was prepared by defatting with petroleum ether for 16 h followed by soxhelation with 70% methanol (1 : 10 w/v) for 24 h, and standardization of the extract was carried out using HPLC with 5-HT as a standard. Electroconvulsions were induced by the maximal electroshock model, and chemoconvulsions were induced by picrotoxin. *Results*. The HPLC chromatogram of the *Ficus benjamina* L. extract showed an absorption peak with a retention time of 1.797 min, similar to that observed with standard serotonin (5-HT) solution. In the maximal electroshock model, FBE significantly reduced the duration of the tonic hind limb extensor and extensor-to-flexor ratio (E/F ratio) in a dose-dependent manner. Moreover, in the picrotoxin-induced seizure model, FBE increased the seizure latency and decreased the duration of tonic-clonic convulsions dose-dependently. We confirmed the anticonvulsant activity of the FBE extract as it attenuated both maximal electroshock and picrotoxin-induced convulsions. *Conclusion*. The *in vivo* studies revealed that the Ficus extract was found to protect the animals in electroshock-induced and picrotoxin-induced convulsions.

1. Introduction

Epilepsy is a neurological disorder, primarily caused by an imbalance between excitatory and inhibitory neurotransmission, which leads to abnormally synchronized firing of groups of neurons [1]. Approximately 50 million individuals worldwide suffer from epilepsy, which is a serious global health issue. It is one of the most widespread chronic neurological conditions in the world and, in some regions, has detrimental physical, financial, and discriminatory effects [2]. After a stroke and Alzheimer's disease, epilepsy is the third most frequent neurological condition [3]. Based on suspected underlying causes, epilepsy is divided into genetic and acquired epilepsy. Genetic epilepsy results from a genetic predisposition of the brain to produce seizures, while acquired epilepsy is due to acute insult or a lesion that alters the cellular, molecular, and physiological properties that give origin to seizures [4]. It has been suggested that altered

neuronal membrane permeability, decreased inhibitory neuronal regulation, or neurotransmitter imbalance may be the probable initiators of seizures, though the precise cellular effect is not fully clear [2].

Current anticonvulsant medicines can effectively manage epileptic seizures in approximately 50% of patients; 25% of cases may improve, while the remaining patients do not benefit appreciably [2]. Furthermore, unwanted side effects of clinically used medications frequently make therapy difficult [5, 6]. Benzodiazepines have dependence liability, along with an increased risk of glaucoma and respiratory depressive effects [5]. Moreover, drugs like carbamazepine cause upset stomach, serious skin reactions, and may reduce sodium levels. Phenobarbital and its derivative treatment can lead to memory loss, sedation, depression, and also possess chances of birth defects [6]. Pregabalin, $\alpha 2\delta$ calcium channel subunit ligand, is often associated with trouble in concentration, sedation, weight gain, and swelling of hands and feet [7].

Medicinal plants are used for the treatment of different infections. These plants contributed as a source of inspiration for novel therapeutic compounds. The medicinal value of plants is due to the presence of a wide variety of secondary metabolites including alkaloids, glycosides, tannins, volatile oil, and terpenoids [8, 9]. Several medicinal plants have been explored for their anticonvulsant activity in various animal models. These include *Carum copticum* [10], *Erythrina mulungu* [11], *Anisomeles malabarica* [12], *Anacyclus pyrethrum* [13], *Zizyphus jujuba*, *Passiflora incarnata* [14], *Acorus calamus, Crocus sativus, Emblica officinalis, Ginkgo biloba, Hypericum perforatum, Matricaria recutita,* and *Panax ginseng* [15]. *Ficus* is a large genus with as many as 800 species [16]. The methanol extract from leaves of *Ficus hispida* has been reported to inhibit chemically induced convulsions in mice [17]. The aqueous extract of roots of *F. religiosa* has been studied for its protective action in strychnine and pentylenetetrazole-induced seizures [18]. Figs of *F. religiosa* have also been documented to have anticonvulsant activity [19]. The anticonvulsant action of most of the *Ficus* species has been attributed to the rich content of serotonin (5-HT) in these plants [18, 19]. The most common cause of mortality in people with refractory epilepsy is sudden unexpected death. The pathophysiology of sudden unexpected death in epilepsy patients is heavily influenced by defects in central respiratory regulation and serotonin (5-HT) system malfunction [20]. Furthermore, it has been reported that the increased serotonin level is associated with a reduced incidence of seizure-related breathing problems in epilepsy patients [21].

Literature evidence delineates that its latex and fruit extracts are used by indigenous cultures to cure skin conditions, inflammation, vomiting, leprosy, malaria, and nasal ailments [22]. Moreover, many parts of the plant have long been widely utilized in traditional medicine to treat skin problems and dysentery [23]. A preliminary investigation of the *Ficus benjamina L.* fig extract revealed the presence of 5-HT. However, to date, no studies have been reported for its anticonvulsant potential. Therefore, the present study is designed to investigate the anticonvulsant effect of ripe figs of *Ficus benjamina* L.

2. Material and Methods

2.1. Drugs and Chemicals. Picrotoxin (Cat No. P1675) and serotonin (Cat No. 14927) were purchased from Sigma Aldrich, USA. All other solvents and chemicals were of analytical grade and purchased from local suppliers.

2.2. Collection of Plant Materials and the Extraction Procedure. Ripe figs of *Ficus benjamina* L. (Moraceae) were collected from the campus of Guru Nanak Dev University, Amritsar, between March and April, washed with water, and shade dried. Dried figs were then ground into a coarse powder. The powdered material was defatted with petroleum ether for 16 h and then extracted by soxhelation with 70% methanol (1 : 10 w/v) for 24 h. The hydroalcoholic extract FBE obtained was filtered, and the solvent was evaporated under reduced pressure using a rotary evaporator (Heidolph Laborota 4001) to obtain a semisolid mass that was stored in an airtight container in a refrigerator till further use. The yield was found to be 15%, w/w. The extract was reconstituted by dissolving it in 10% (v/v) dimethyl sulfoxide. Thereafter, it was suspended in 0.5% carboxymethylcellulose (DMSO 1: CMC 9) for a treatment purpose [19].

2.3. Preliminary Phytochemical Screening of FBE. Preliminary phytochemical screening of FBE was carried out to detect the presence of alkaloids, glycosides, tannins, saponins, etc.

2.4. HPLC Characterization of FBE. FBE was standardized w.r.t. the content of 5-HT as discussed in other species of *Ficus* [24]. 2 mg of pure 5-HT was dissolved in 100 mL of methanol and used as a standard; 50 mg of the *F. benjamina* extract was dissolved in 50 ml of methanol to prepare a sample solution (1 mg mL^{-1}). The solution was then centrifuged at $4500 \times g$ for 10 min, and the supernatant was used for further detections. The standard and sample solutions were filtered through a 0.45 μm membrane filter separately. The UV spectrum of pure 5-HT was determined by using a spectrophotometer with a scanning wavelength of 200–400 nm. Separation was performed on a 250 mm × 4.6 mm (5 μm particles) Hypersil GOLD C-18 RP column from Thermo Incorporated using 25 mM phosphate buffer (pH 2.5) and acetonitrile at 95 : 5 (v/v) at a flow rate of 1 mL min^{-1}. The injection volume was 10 μL, and the peaks were identified by comparison with the retention times of the standard solution.

2.5. Animals. Swiss albino mice of either sex were used in the present study. The animals were procured from Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana, Punjab, and housed in the central animal house of Guru Nanak Dev University, Amritsar. Animals had free access to food (standard laboratory chow diet) and water and were maintained at a temperature of 24 ± 4°C in a 12-hour dark-light cycle. The protocol (Approval no. 1009/BT/Dated Aug 2011, Protocol No. 20) was approved by the institutional

animal ethics committee and was in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

2.6. Assessment of Anticonvulsant Activity. The animals were divided into 11 groups ($n = 6$) for the anticonvulsant study using maximal electroshock and picrotoxin-induced convulsion models as described below. FBE, picrotoxin, diazepam, and phenytoin were suspended in freshly prepared 1% carboxymethylcellulose (CMC). All the drugs were administered intraperitoneally. The schematic protocols are shown in Figure 1.

2.7. Maximal Electroshock-Induced Convulsions. A total of five groups (Figure 1) were studied according to the method in [25]. In each group, animals received the respective treatment for 30 min before an electric shock of 50 mA for 0.2 s through corneal electrodes using an electroconvulsiometer (INCO, Ambala, India); the duration of tonic hind limb extension was determined followed by recovery or death.

2.8. Picrotoxin-Induced Convulsions. A total of five groups (Figure 1) were included in picrotoxin-induced seizures according to the method described by [25]. Picrotoxin (5 mg kg^{-1}) was injected 30 min after the respective treatment in each group. The onset of mild jerks, tonic-clonic convulsion, and duration of convulsions were noted in all groups and compared with those in the vehicle-treated control.

2.9. Statistical Analysis. All results are expressed as the mean ± standard error of the mean (SEM). Statistical analysis was performed by the one-way analysis of variance (ANOVA), followed by post hoc analysis and Tukey's test using InStat software version 3.05 (Graphpad Inc., San Diego, USA). The Design-Expert 10.0 software (Stat-Ease, Inc.) was used to analyze the results of the response surface design.

3. Results

3.1. Preliminary Phytochemical Analysis of FBE. The hydroalcoholic extract of *F. benjamina* was found to contain saponins, flavonoids, tannins, alkaloids, and carbohydrates.

3.2. HPLC Standardization of FBE. The HPLC chromatogram of the standard 5-HT solution showed an absorption peak with a retention time of 1.797 min (Figure 2(a)). A similar peak was observed in the HPLC chromatogram of FBE at the same retention time, indicating the presence of 5-HT in the extract (Figure 2(b)) (Table 1).

3.3. Effect of Various Pharmacological Interventions on Maximal Electroshock-Induced Seizures. The treatment of mice with an electric shock of 50 mA for 0.2 s was found to produce the flexor and tonic hind limb extensor, followed by stupor or death. Maximal electroshock produced a tonic hind limb extensor of an average duration of 11.2 ± 0.8 s in the vehicle-treated control with a percentage mortality of 83.3%. Treatment with phenytoin was found to completely abolish the extensor phase with no mortality. The treatment with FBE was found to produce a decrease in the duration of the tonic hind limb extensor and the extensor-to-flexor ratio (E/F ratio) significantly and in a dose-dependent manner (Figures 3(a) and 3(b)). The percentage protection with FBE 400 mg kg^{-1} treatment was found to be 92.8 ± 11.6% (Figure 3(c)).

Treatment of animals with picrotoxin was found to precipitate tonic-clonic (T/C) convulsions after 11.9 ± 2.6 min in the vehicle-treated control group, and the duration of T/C convulsions was found to be 16.6 ± 1.5 s. Treatment with diazepam was found to completely abolish picrotoxin-induced convulsions (zero convulsions). Therefore, no latency was observed in the diazepam group, whereas FBE was found to produce a dose-dependent increase in seizure latency and a decrease in the duration of T/C convulsions at doses of 100, 200, and 400 mg kg^{-1} (Figures 4(a) and 4(b)). The respective percentage of protection was found to be 22.8, 44.5, and 66.2% (Figure 4(c)). The effect was statistically significant as compared to the vehicle control.

4. Discussion

Conventional anticonvulsant therapy is marred by several adverse drug reactions including cognitive deficits, teratogenicity, and behavioral and cosmetic side effects [26, 27]. These problems have led to a renewed interest in plant-based medicines due to their better tolerability and lower number of side effects. Plants have been used as medicine to maintain human health for ages and are also major natural sources of medicinal compounds in current pharmacopoeias [28, 29]. The current study demonstrated the protective effect of the hydroalcoholic fig extract of *Ficus benjamina* L. (FBE) on picrotoxin and maximal electroshock-induced convulsions in mice. FBE was found to produce a dose-dependent reduction in convulsions.

The HPLC investigation revealed the presence of 5-hydroxytryptamine (5-HT) in the extract. Earlier studies have revealed the presence of 5-HT in the figs of *Ficus religiosa* [30]. Although there are conflicting reports on the role of 5-HT in epilepsy [24], there is sufficient evidence in the literature that supports the inhibition of 5-HT reuptake to have beneficial effects in epilepsy. Selective serotonin reuptake inhibitors (SSRIs) have been documented to help treat epilepsy [31, 32]. Some agents like 5-hydroxytryptophan that increases the extracellular level of 5-HT have been found to inhibit focal and generalized seizures, and depletion of 5-HT evokes seizures [33]. Serotonergic neurotransmission has been documented to modulate a variety of experimentally induced seizures and drugs that increase the concentration of 5-HT to have an anticonvulsant effect [34]. It is reported that serotonergic agonists can directly affect the firing of cerebellar neurons and can

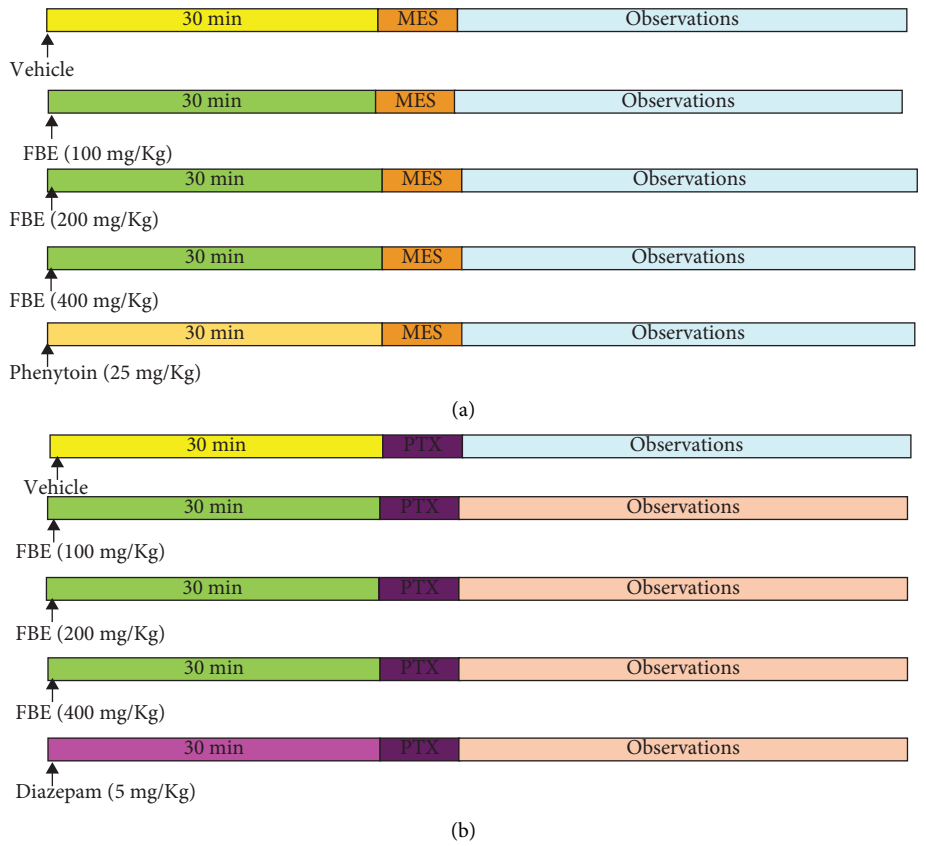

Figure 1: Schematic protocols for anticonvulsant activity of *Ficus benjamina* L. in (a) maximal electroshock-induced convulsions and (b) picrotoxin-induced convulsions in mice.

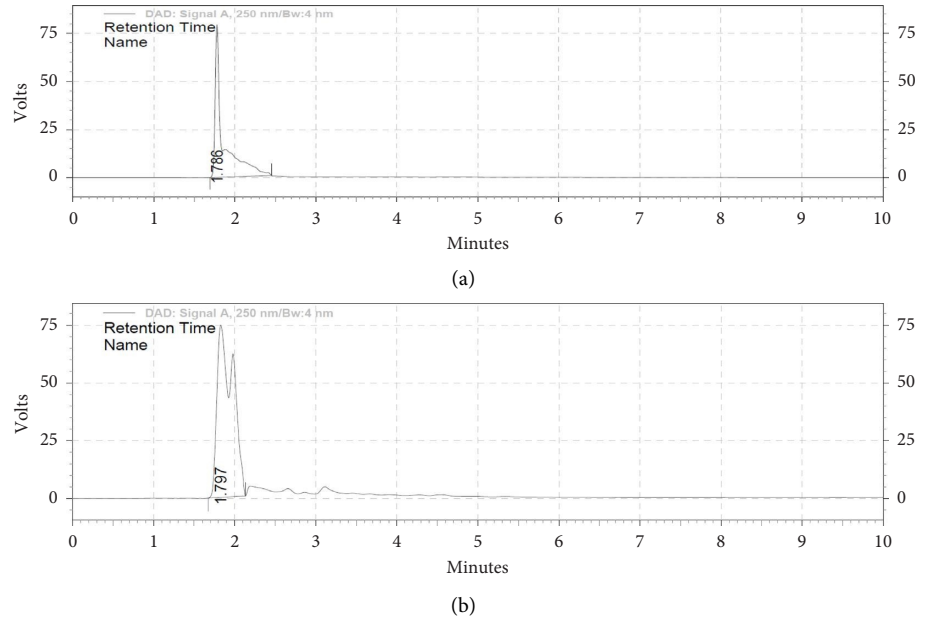

Figure 2: (a) HPLC of the 5-HT standard; (b) HPLC of the *Ficus benjamina* L. extract.

modulate the effect of excitatory amino acids [35]. In the genetic model of absence epilepsy, it is found that there is an interaction of glutamatergic and serotonergic mechanisms in the regulation of epileptic activity [33]. All the brain areas that are involved in epilepsy have an expression of 5-HT receptors, and currently, the role of 5-HT_{1A}, 5-HT_{2C}, 5-HT_3,

Table 1: HPLC data depicting the comparison of the standard and the extract.

	Retention time	Area	Area%	Height	Height%
Standard	1.786	1096963	100	166056	100
Extract	1.797	2129641	100	156272	100

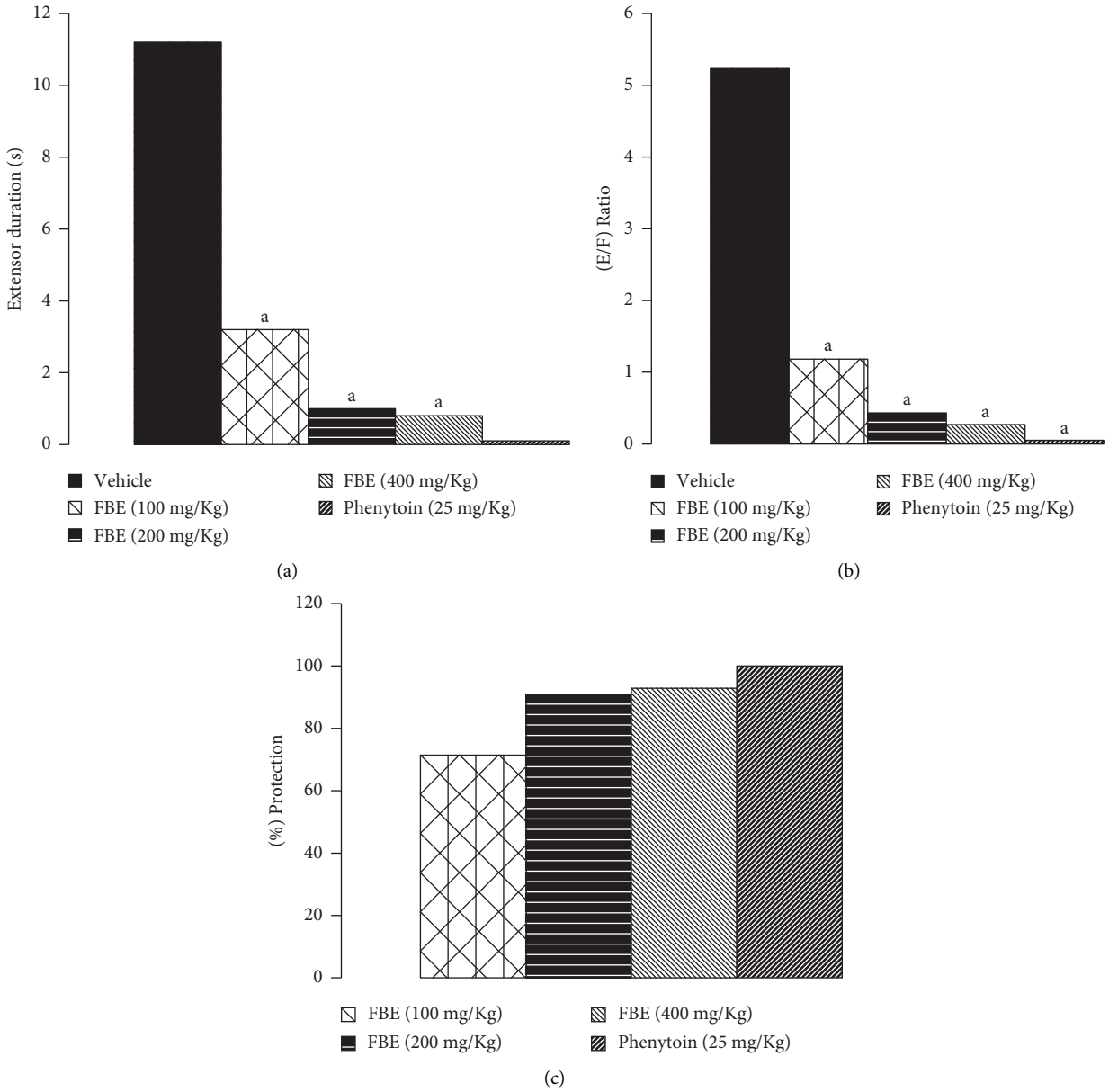

Figure 3: Effect of various pharmacological interventions on maximal electroshock-induced seizures. (a) Duration of the extensor, (b) extensor/flexor ratio, and (c) % protection. All values are expressed as the mean ± SEM. $^a p < 0.001$ compared to the vehicle control. The effect of various pharmacological interventions on picrotoxin-induced seizures.

and 5-HT_7 receptors has been described in epilepsy [33]. In general, hyperpolarization of glutamatergic neurons by 5-HT_{1A} receptors and depolarization of GABAergic neurons by 5-HT_{2C} receptors, as well as antagonists of 5-HT_3 and 5-HT_7 receptors, decrease neuronal excitability [32]. Various studies on experimental animals have reported that the activation of 5-HT_{2C} and 5-HT_7 receptors have an anticonvulsant effect [34]. The postictal phase is marked by a decrease in the 5-HT transporters in the brain and a decrease in the brain levels of tryptophan, the precursor of 5-HT, which is suggested to be related to some types of epilepsy [31]. The conventional antiepileptic therapy with drugs such as phenytoin and valproic acid is effective in treating the episodes of convulsions but is insufficient to manage

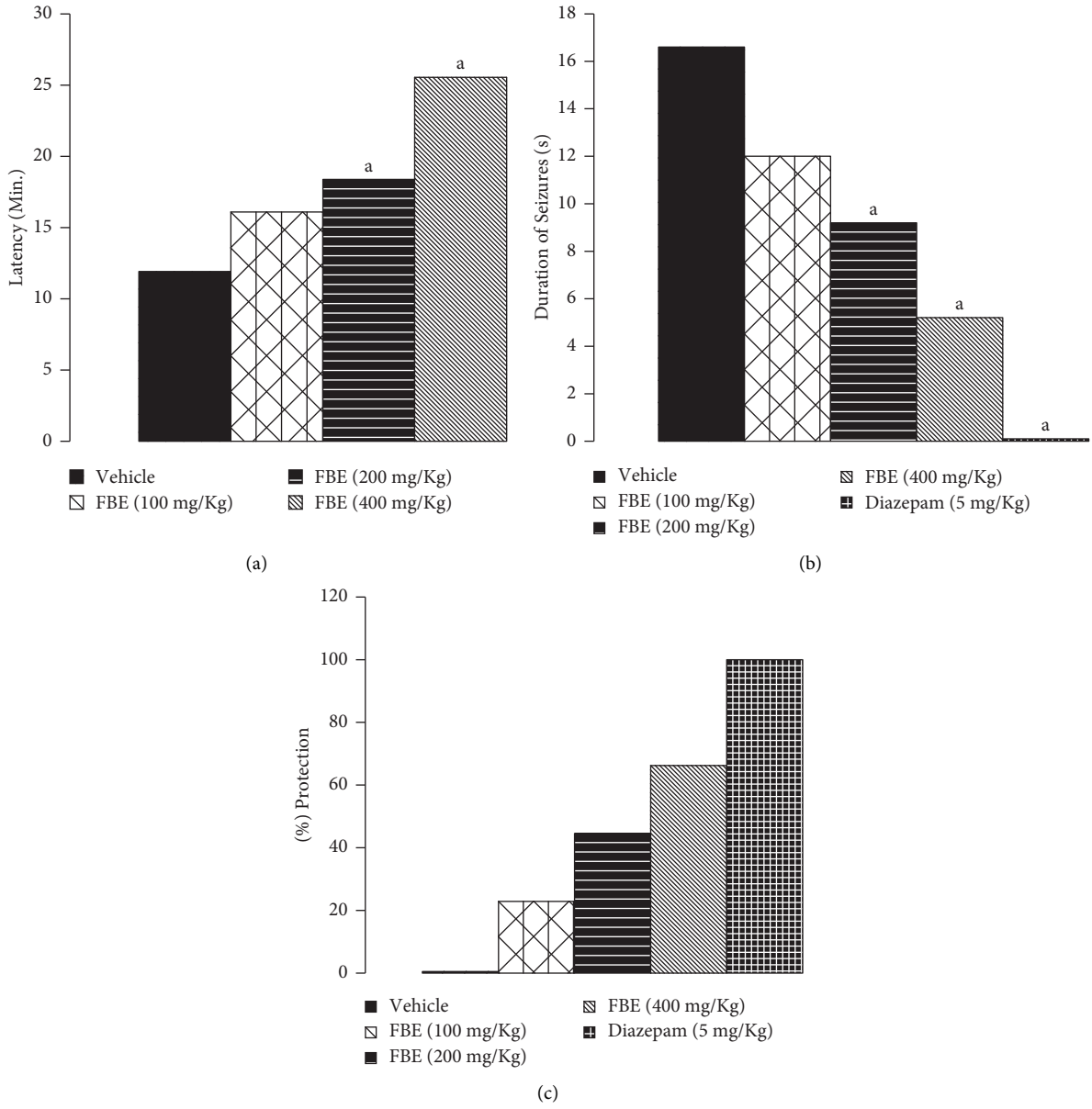

Figure 4: Effect of various pharmacological interventions on picrotoxin-induced seizures. (a) Latency to convulsions, (b) duration of convulsions, and (c) % protection. All values are expressed as the mean ± SEM. $^a p < 0.001$ compared to the vehicle control.

postictal depression. 5-HT present in FBE may act to replenish the depleted 5-HT levels in the brains of epileptic patients. The current study only screened the anticonvulsant activity of the *Ficus benjamina* L. extract along with determination of serotonin in the extract. One of the limitations of the current study is that only the activity of the hydroalcoholic extract was performed, and second, apart from serotonin, the estimation of other components of interest was not carried out. However, this study will give a base for researchers to perform the isolation of molecules of interest from this plant and further explore their potential in epilepsy.

5. Conclusion

Overall, the outcomes of the current investigation delineate that the hydroalcoholic fig extract of *Ficus benjamina* L. (FBE) exerted a protective effect against picrotoxin and maximal electroshock-induced convulsions in mice dose-dependently. The anticonvulsant effect of the *Ficus benjamina* L. extract might be attributed to the presence of 5-HT in the extract. However, this needs more direct and detailed studies to prove this contention. In terms of future prospects, it is necessary to continue the development of efficacious anticonvulsant agents that are cost-effective with

minimal side effects. Based on the outcome of the current study, it seems logical to presume that *Ficus benjamina* L. may contain some molecules which might have anticonvulsant activity. Characterization of secondary metabolites will reveal further health benefits.

Data Availability

Data used in this study are available on request to the corresponding author.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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