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Dual Protective Effect of *Cynodon dactylon* in Epilepsy as Well as Depression

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ABSTRACT

Background and Objective: Depression and epilepsy are considered as the strongest predictor of poor quality of life. A complex relation has been established between the two conditions which suggest that the high co morbidity of depression and epilepsy is related to the existence of common neurobiologic and pathogenic mechanisms involved in them. Plants and their extracts are better choice to treat such type of diseases (in which treatment of one worsens the other), because of presence of antagonistic substances in them, due to which they show lesser or no side effects. Hence, the present study was designed to investigate the effect of ethanolic extract of *Cynodon dactylon* on epilepsy and depression in mice. **Methodology:** Antidepressant activity was investigated using forced swim test and reserpine induced hypothermia model and antiepileptic activity was explored using MES test and PTZ induced seizure test. **Results:** The results of the present study showed that ethanolic extract of *C. dactylon* possess promising antidepressant as well as antiepileptic activity. From the mechanistic study performed using baclofen induced catatonia and lithium induced head twitch model, it was demonstrated that the antiepileptic effect of *C. dactylon* may be mediated through its GABA-mimetic action and antidepressant activity may be mediated through 5 HT_2 antagonistic action (like atypical antidepressants). **Conclusion:** Thus, it may be concluded that dual protective effect of *C. dactylon* in epilepsy and depression is associated with diverse mechanism, namely GABA-mimetic and 5-HT_2 antagonistic action.

Key words: *Cynodon dactylon*, epilepsy, depression

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INTRODUCTION

Central Nervous System (CNS) disorders are some of the most widespread, disturbing and yet poorly treated ailments. The advancement in new drug therapies for CNS disorders such as depression, anxiety, psychosis, schizophrenia, pain, epilepsy and Alzheimer's disease provided patients with noteworthy improvement in quality of life as well as reduced the future economic burden on health-care systems. Out of these above mentioned CNS disorders, depression and epilepsy are considered as the strongest predictor of poor quality of life. This suggests that there is a substantial need for approaches to enhance the output of research and development in this field.

Depression is a common mental disorder characterized by depressed mood, loss of interest or pleasure, diminished energy, feelings of guilt or low self-worth, uneasy sleep or appetite and poor attention. According to WHO[1] report, depression is a common illness worldwide, with an estimated 350 million people affected with it[1]. Epilepsy is another most common and important chronic medical problems. The prevalence of epilepsy in the general population is approximately 8.2 per 1000. Epilepsy is defined as occurrence of persistent seizures due to abrupt electrical misfiring of neurons or nerve cells in the epileptic brain. However, it is complicated by a high rate of behavioral or psychiatric co-morbid symptoms and disorders like depression, anxiety, psychosis, obsessive-compulsive disorder, attention deficit and personality disorders, aggression and suicide[2].

Depression in epilepsy has been considered, for a long time, as a complication of the underlying seizure disorder. A complex relation has been established between the two conditions in research studies published in the last decade which suggests that the high comorbidity of depression and epilepsy is related to the existence of common neurobiologic and pathogenic mechanisms involved in them. In addition, depression

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continues to be identified as one of the most important causes of poor quality of life of Patients With Epilepsy (PWE), which exceeds the impact of seizure frequency and severity in patients with treatment resistant epilepsy. Yet, despite its high prevalence, depression remains under recognized and under treated. In addition to studies of people with existing epilepsy, depression has been examined as a risk factor for developing epilepsy. Such studies find that depression augments the threat of epilepsy, raising the likelihood that depression and epilepsy contribute to a common pathophysiology. It has been known for a long time that there are relations between epilepsy and depression and there are several reasons why the two disorders may be closely linked. Previously, it was believed that depression either is causally related to the epilepsy or occurs secondarily on account of the socially detrimental nature of epilepsy. However, recent epidemiologic studies propose a bidirectional relation with a high occurrence of secondary epilepsy in primarily depressed patients[3].

Several studies have noted an association between depression and seizure frequency. In an epidemiological study, it was observed that depression occurred in 4% of seizure-free patients and in 10% of patients suffering less than one seizure a month, but at a rate of 21% in patients with higher seizure frequency. It was observed that patients with epilepsy and continuing seizures were significantly more likely to suffer from depression than those in remission[4].

All these issues indicate an unmet need for the discovery of remedies to treat depression in epilepsy, without affecting seizures threshold. In spite of all the amazing development in modern medication, traditional medicine has always attracted research workers and has also been used in clinical practice[5]. Medicinal plant research has progressed constantly demonstrating the pharmacological effectiveness of different plant species in a variety of animal models in the search for new therapeutic products for the treatment of CNS disorders worldwide[6]. Plants and their extracts are better choice to treat such type of diseases (in which treatment of one worsens the other), because of presence of antagonistic substances in them, due to which they show lesser or no side effects[7]. While searching some herbal remedies, it has been found that literature reports pertaining to the ethnomedical use of *Cynodon dactylon* in treatment of epilepsy and depression.

Hence, the present study was designed to investigate effect of ethanolic extract of *Cynodon dactylon* on epilepsy and depression in mice. This was the first attempt made to explore the dual protective effect of *Cynodon dactylon* in epilepsy and depression.

MATERIALS AND METHODS

Plant materials: The plant material was collected from local nursery, Pune district. The plant material was identified and authenticated by Botanical Survey of India, Pune. The voucher specimen of the same was deposited in Botanical Survey of India (BSI/WRC/TECH/2013).

Drugs and chemicals: Pentylenetetrazole, Imipramine, Risperidone, Diazepam and Phenytoin were obtained from Oswal Chemical industries, Pune. Reserpine was obtained from Sigma Aldrich.

Preparation of extract: The whole plant of *Cynodon dactylon* (1 kg) was shade dried, powdered and sieved through 40 mesh size of sieve. The powdered plant materials was extracted with petroleum ether (40-60°C) followed by ethanol. The ethanolic extract of *C. dactylon* was evaporated to dryness under vacuum (CDE).

Phytochemical analysis: The ethanol extract of *Cynodon dactylon* (CDE) was subjected to preliminary phytochemical tests to determine the presence of various phytoconstituents and was used for further experimental study.

Animals: Behavioral experiments were carried out using Swiss Albino mice. They were procured from Haffkine Institute, Mumbai. Animals were housed under standard laboratory conditions (temperature 23±2°C and relative humidity 60±10%) maintained on 12:12 h light: dark cycle with free access of standard diet and filtered water. The experimental procedures on animals were in compliance with the Institutional Animal Ethics Committee.

Assessment of antidepressant activity

Reserpine induced hypothermia: Swiss Albino mice (body weight: 19-21 g) were used. On the day before testing, animals were administered 2 mg kg^{-1} reserpine subcutaneously. They were housed in a climate controlled animal colony and gave free access to food and water. Eighteen hours after reserpine administration, the animals were placed into individual cages. The initial rectal temperature was determined by insertion of an electronic thermometer to a constant depth of 2 cm. Imipramine (10 mg kg^{-1}, i.p.) and CDE (25, 50 and 75 mg kg^{-1}, i.p.) were administered and the rectal temperature was measured again at 60 min intervals for 7 h[8].

Forced swim test: Animals were divided into 6 groups (n = 6) and treated with vehicle, Imipramine (10 mg kg^{-1}, i.p.) and CDE (25, 50 and 75 mg kg^{-1}, i.p.). Mice were individually forced to swim in open glass chamber (25×15×25 cm) containing fresh water to height of 15 cm and maintained at 26±1°C. At this height of water, animals were not able to support themselves by touching the bottom of side walls of the chamber with the hind-paw or tail. The duration of immobility was recorded during total 6 min period. Mice were considered to be immobile when they ceased struggling and remained floating motion less in water, making those movements necessary to keep their head above water. Following swimming session mice were towel dried and returned to their housing conditions[8].

Assessment of antiepileptic activity

Maximal electroshock induced convulsion (MES): Groups of male Swiss mice (18-30 g) each containing six animals were used. Animals were treated with vehicle, Phenytoin (25 mg kg^{-1}, i.p.) and CDE (25, 50 and 75 mg kg^{-1}, i.p.). The test was started 30 min after i.p. treatment with the test compound or the vehicle. An apparatus with corneal electrodes was used to deliver the stimuli. The intensity of stimulus 12 mA, 50 Hz for 0.2 sec was used. Under these conditions, all vehicle treated mice showed the characteristic extensor tonus[8].

Pentylenetetrazole induced convulsion (PTZ): Mice of either sex with a body weight between 18 and 22 g were used. Animals were pretreated with diazepam (1 mg kg^{-1}, i.p.) and CDE (25, 50 and 75 mg kg^{-1}, i.p.) and after 30 min; PTZ (60 mg kg^{-1}) was administered subcutaneously. Each animal was placed into an individual plastic cage for observation lasting 1 h onset and duration of tonic-clonic seizures were recorded[8].

Mechanistic study

Baclofen induced catatonia: Mice of either sex with a body weight between 18-22 g were used. Animals were pretreated with vehicle, CDE (25, 50 and 75 mg kg^{-1}, i.p.) followed by baclofen (10 mg kg^{-1}, i.p.) after 30 min. The duration of catatonia was measured up to 2 h[9].

Lithium induced head twitches: The animals were divided into five groups, each containing six animals. They were treated with vehicle, risperidone (2 mg kg^{-1}), CDE (25, 50 and 75 mg kg^{-1}, i.p.) Thirty minute after treatments, lithium sulfate (200 mg kg^{-1} i.p.) was administered. The number of head twitches was observed for 60 min after the administration of lithium sulfate[10].

RESULTS

Phytochemical analysis: Preliminary phytochemical screening of ethanolic extract of *Cynodon dactylon* showed the presence of alkaloid, glycosides, flavonoids and steroids.

Antidepressant activity: Antidepressant activity was investigated using forced swim test and reserpine induced hypothermia model. In present study, treatment with reserpine induced significant hypothermia ($p<0.01$) compared to normal control group. Animal treated with imipramine (10 mg kg^{-1}, i.p.) showed significant ($p<0.01$) reversal of reserpine induced hypothermia. Treatment with CDE (25, 50 and 75 mg kg^{-1}) significantly ($p<0.01$) reversed reserpine induced hypothermia as shown by increased rectal temperature compared to reserpine control group (Fig. 1). Imipramine (15 mg kg^{-1}, i.p.) does not show significant change in the locomotor activity as compared to the vehicle group. Similarly, treatment with CDE (25, 50 and 75 mg kg^{-1}, i.p.) induced no significant change in locomotor activity as compared to vehicle group (Fig. 2).

In FST, in vehicle treated group, the duration of immobility was observed to be 126.83±15.2 min. Treatment with CDE (50 and 75 mg kg^{-1}) significantly ($p<0.05$) decreased the duration of immobility in dose dependent manner compared to vehicle treated group, while treatment with CDE (25 mg kg^{-1}) showed insignificant decrease in duration of immobility. Animal treated with imipramine (10 mg kg^{-1}, i.p.) showed significant ($p<0.01$) decrease in duration of immobility (Fig. 3). The treatment with CDE (25, 50 and 75 mg kg^{-1}, i.p.) did not show significant change in locomotor activity as compared to vehicle group after FST. The imipramine (15 mg kg^{-1}, i.p.), also did not showed significant change in the locomotor activity as compared to the vehicle group (Fig. 4). Thus, the results signified that CDE possess significant antidepressant activity.

Antiepileptic activity: Antiepileptic activity was explored using MES test and PTZ induced seizure test. In present study, in vehicle treated group, MES induced significant convulsions. Phenytoin (25 mg kg^{-1}, i.p.) decreased the duration of tonic hind leg extension significantly ($p<0.01$). Treatment with CDE at doses of

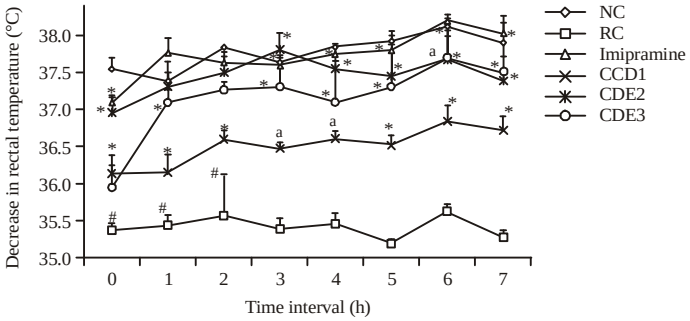

Fig. 1: Effect of CDE on reserpine induced hypothermia, #p<0.01 (ANOVA followed by Dunnett's test) compared with control treated group, ap<0.05 (ANOVA followed by Dunnett's test) compared with reserpine control group, ⋆p<0.01 (ANOVA followed by Dunnett's test) compared with reserpine control group

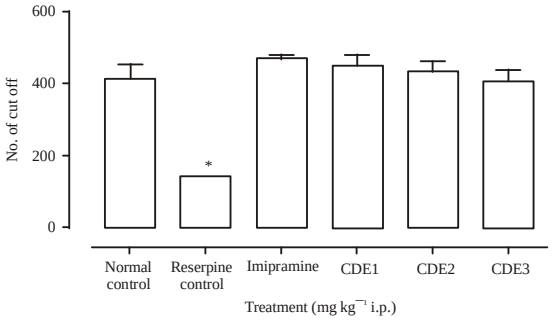

Fig. 2: Effect of CDE on locomotor activity after reserpine induced hypothermia, ⋆p<0.01 compared with normal control (ANOVA followed by Dunnett's test)

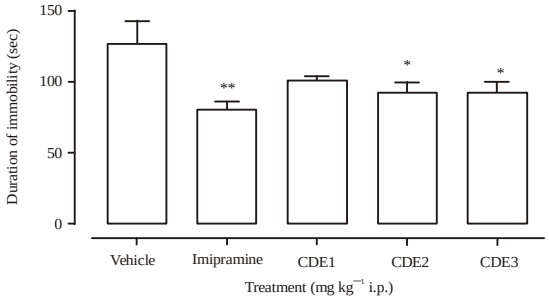

Fig. 3: Effect of CDE on duration of immobility in forced swim test, ⋆p<0.05, compared with vehicle treated group, ⋆⋆p<0.01, compared with vehicle treated group (ANOVA is followed by Dunnett's test)

25, 50 and 75 mg kg^{-1} significantly (p<0.01) reduced the duration of tonic hind leg extension as compared to vehicle treated group (Fig. 5). In PTZ test, treatment

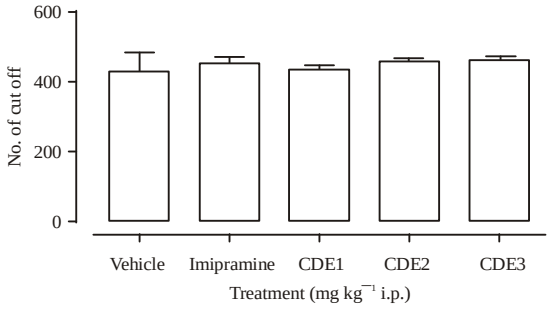

Fig. 4: Effect of CDE on locomotor activity after forced swim test

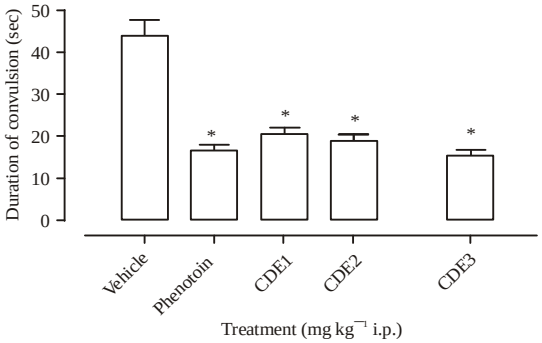

Fig. 5: Effect of CDE on duration of convulsions in MES test, ⋆p<0.01 compared to vehicle group (ANOVA followed by Dunnett's test)

with CDE at doses of 25, 50 and 75 mg kg^{-1} significantly (p<0.01) delayed the onset of convulsions and decreased the duration of convulsions significantly (p<0.01) in dose dependent manner compared to vehicle treated group. Animal treated with diazepam (1 mg kg^{-1}, i.p.)

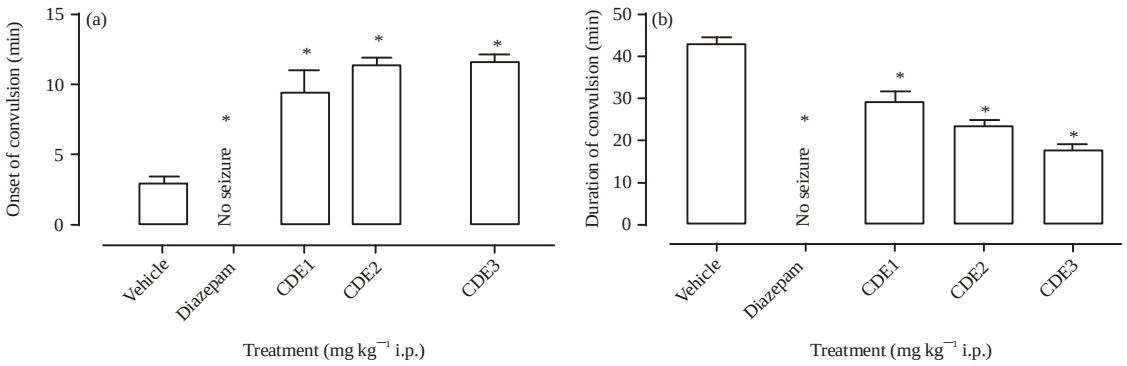

Fig. 6(a-b): Effect of CDE, (a) On onset and (b) On duration of convulsion in PTZ induced convulsion, ⋆p<0.01 compared with vehicle treated group (ANOVA followed by Dunnett's test)

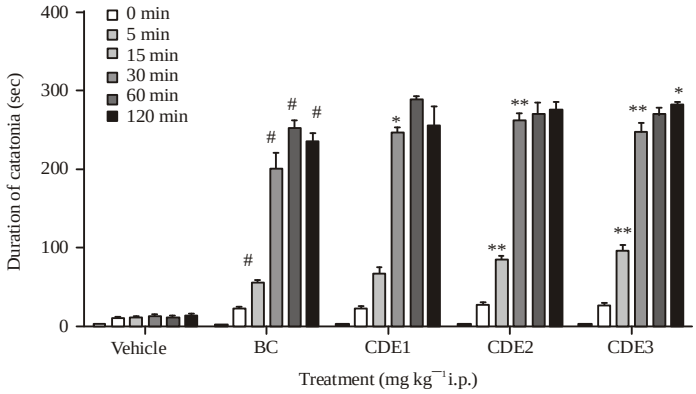

Fig. 7: Effect of CDE on baclofen induced catatonia, #p<0.01 compared with vehicle treated group, *p<0.05 compared with baclofen control group, **p<0.01 compared with baclofen control group (ANOVA is followed by Dunnett's test)

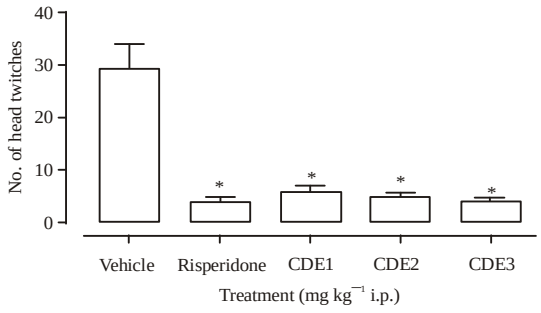

Fig. 8: Effect of CDE on lithium induced head twitches, *p<0.01 compared with vehicle treated group (ANOVA is followed by Dunnett's test)

have shown 100% protection against PTZ induced seizures (Fig. 6a and b). These results suggested that CDE possess significant antiepileptic activity.

Mechanistic study: Mechanistic study was carried out using baclofen induced catatonia and lithium induced head twitches. Baclofen (20 mg kg^{-1}) induced significant catatonic effect in animals from 30 min onward. Pretreatment with CDE (25, 50 and 75 mg kg^{-1}, i.p.) also induced catatonic effect. In addition, pretreatment with CDE (25, 50 and 75 mg kg^{-1}, i.p.) preponed catatonic effect significantly ($p<0.01$) indicating its GABA-mimetic potential (Fig. 7).

In present study, lithium sulphate (200 mg kg^{-1}) induced significant head twitches in vehicle treated animals. Risperidone (2 mg kg^{-1}, i.p.) significantly reduced ($p<0.01$) the lithium induced head twitches as compared to the vehicle group. Similarly, pretreatment with CDE (25, 50 and 75 mg kg^{-1}, i.p.) reduced number of head twitches significantly ($p<0.01$) compared to vehicle group which revealed that CDE possess 5-HT_2 antagonistic action (Fig. 8). The result of

mechanistic model indicates that antidepressant and antiepileptic activity of CDE may be associated with its GABA-mimetic and 5-HT_2 antagonistic action.

DISCUSSION

The present study was designed to evaluate antidepressant activity of ethanolic extract of *Cynodon dactylon* (Pers.) by using forced swim test and reserpine induced hypothermia. Forced swim test is widely used as reliable animal model of depression to screen new antidepressants as well as to investigate the mechanisms underlying the action of antidepressants[11]. Several studies have reported that there is decrease in the duration of immobility during the FST test indicating the antidepressant activity of a compound. In the present study, CDE (25, 50 and 75 mg kg^{-1}) significantly decreased the duration of immobility in FST. This indicates that CDE possess significant antidepressant activity. Since the forced behavioral experiment was affected by changes in locomotor activity, an additional experiment was carried out with the specific aim of monitoring the activity. Hence, the antidepressant effect of *C. dactylon* was further confirmed by its effect on locomotor activity using actophotometer after forced swim test. It was observed that CDE did not alter locomotor activity. These result supports that the effect of CDE in forced swim test may be due to its antidepressant activity and not due to its locomotor behavior.

Reserpine-induced hypothermia is another mechanistic model for the confirmation of antidepressant action. In synaptic vesicles, reserpine, a monoamine depleting agent blocks the monoamine transport and leads to monoamine depletion. The depletion of brain 5-HT affects the central nervous system characterized by hypothermia[12]. Decrease in body temperature induced by reserpine has been reported to be antagonized by antidepressants[13]. It has been reported that ethanolic extract of aerial part of *Cynodon dactylon* increased catecholamine such as (epinephrine, norepinephrine, dopamine and serotonin) level in mice[14]. In the present study, CDE (50 and 75 mg kg^{-1}) significantly reversed reserpine induced hypothermia indicating antidepressant effect of CDE. Thus, it may be concluded that CDE possess significant antidepressant activity which may be associated with increase in brain catecholamine level. This result was in accordance with the previous finding

Further, antiepileptic activity of ethanolic extract of whole plant of *Cynodon dactylon* (Pers.) in mice was evaluated using Maximal Electroshock induced convulsion (MES) and Pentylenetetrazole induced convulsion. The MES is a standard procedure that evaluates the testing materials ability to protect against hind limb extension in MES. In present study, CDE (25, 50 and 75 mg kg^{-1}) significantly decreased the total duration of hind limb extension as compared to vehicle treated group. This suggests that CDE possess significant anticonvulsant activity and may be useful for the management of generalized tonic-clonic and partial seizures.

It has been known for a number of years that PTZ inhibits GABA-activated channels[15]. The effect of most of antiepileptic agents is to enhance the response to GABA, by facilitating the opening of GABA-activated chloride channels. It is well documented that PTZ/INH-induced convulsions are produced due to alteration of GABA level in brain[16]. PTZ induced seizures can be prevented by drugs that enhance gamma amino butyric acid type-A ($GABA_A$) receptor mediated inhibitory neurotransmission such as benzodiazepines and phenobarbital[17]. In present study, CDE (25, 50 and 75 mg kg^{-1}) significantly increased the onset and reduced the duration of PTZ induced seizures. Thus, the results of present study confirmed the antiepileptic potential of CDE.

GABAergic mechanisms are important in the pathogenesis of epilepsy[18]. Inhibition of GABA neurotransmission and enhancement of the action of glutamic acid have been shown to be the underlying factors in epilepsy[19]. Newer antiepileptics namely, Vigabatrin, Tiagabine, Gabapentin, Topiramate, etc acts by increasing GABA levels in the brain by different mechanisms[20]. Therefore, to study mechanism of action of antiepileptic activity of CDE, effect of CDE on baclofen induced catatonia-a GABA mediated behavior was explored. Baclofen is structurally similar to the inhibitory neurotransmitter, GABA and stimulates GABA receptors[18]. In present study, CDE (25, 50 and 75 mg kg^{-1}) significantly preponed baclofen induced catatonia at 30 min interval indicating GABA mimetic action of CDE. Hence, it could be concluded that CDE has antiepileptic activity which is probably associated with its GABA mimetic action.

The antiepileptic drugs most often associated with the occurrence of depressive symptoms seem to be those that act at the benzodiazepine-GABA receptor complex and include barbiturates, tiagabine, topiramate and vigabatrin. In psychiatric practice, it is known that benzodiazepines and other GABA agonists are clinically associated with depression that cause abnormalities of cerebrospinal fluid and GABA have been reported in

patients with depression. Thus, there is the link between sudden cessation of seizures (antiepileptic action), GABAergic agents (GABA mimetic action) and the onset of depression[21]. In the present study, CDE showed significant antidepressant activity as well as antiepileptic activity which we co-related with its GABA mimetic action. These findings made this possible to study involvement of other neurotransmitters like serotonin (5-HT) responsible for the antiepileptic as well as antidepressant action of CDE.

Many evidences in scientific literature had proved the involvement of 5-HT_2 receptors in antidepressant action of drugs as stated below:

- A role for 5-HT_2 receptors in the action of some antidepressants has been shown[22,23]. There are studies showing that 5-$HT_{2A/2C}$ antagonism has a significant role in the mechanism underlying the antidepressant-like effect of conventional antidepressants in the FST. The down regulation of 5-HT_{2A} receptors is proposed to mediate the long-term actions of antidepressants[24,25]
- In recent years, a number of open-label and placebo controlled studies have suggested that atypical antipsychotic drugs and some antidepressants (e.g., mirtazapine and mianserin) augment the clinical response to SSRIs in treatment-resistant patients[26-29]. One common feature of these agents is their ability to occupy 5-HT_2 receptors in the brain at clinical doses and to block 5-HT_2-mediated responses, in particular those mediated by 5-HT_{2A} receptors[30]. Likewise, many antidepressants down regulate 5-HT_{2A} receptors after repeated treatment. Altogether, these observations support a role for 5-HT_{2A} receptors in antidepressant drug action[31]. Some atypical antidepressants like trazodone are believed to act by influencing serotonin receptor sub type 5-$HT_{2A/2C}$. Trazodone's most potent binding property is 5-HT_{2A} antagonism. Trazodone is a metabolite of m-chloro phenyl piperazine (mCPP). Reflex activation of 5-$HT_{2A/2C}$ receptor exerts antidepressant action and is approved clinically[32]. It is of interest to note that 5-HT_{2A} sub type receptors are also located on GABAergic interneuron's in brain and their activation enhances GABA release leading to decreased firing from involved neurons[33]
- When serotonin levels rise after SERT inhibition, 5-HT_{2A} receptors will excite pyramidal neurons and thus mitigate the theoretically desirable 5-HT_{1A} mediated inhibition of these neurons. On the other hand, when 5-HT_{2A} receptors are blocked at the same time that 5HT_{1A} receptors are activated, this potentiates rather than reduces the inhibition of cortical pyramidal neurons, hypothetically mediating synergistic antidepressant effects[34]
- Another mechanism whereby 5-$HT_{2A/2C}$ antagonists could mediate antidepressant effects is by raising the levels of the neurotransmitters dopamine and norepinephrine in the prefrontal cortex. This mechanism has been postulated to explain in part the antidepressant actions of some atypical antipsychotics with 5-HT_{2A} antagonist properties as well as the antidepressant properties of the 5-HT_{2C} antagonists. 5-HT_{2A} and 5-HT_{2C} receptors regulate the release of dopamine and norepinephrine in the cortex, generally inhibiting the release of these neurotransmitters, sometimes via an inhibitory GABA-ergic interneuron. These various pharmacological mechanisms which suggest the way in which 5-$HT_{2A/2C}$ antagonists could be antidepressants in themselves. Nevertheless, this notion is consistent with observations that atypical antipsychotics, which have 5-HT_{2A} antagonist effects as a prominent property, do potentiate the actions of SSRIs/SNRIs in certain depressed patients, especially those who have treatment resistant depression and the observation that several agents with 5-HT_{2C} antagonist actions are approved antidepressants[34]

In order to investigate the possible involvement of the serotonergic system in the antidepressant and antiepileptic activity of CDE, the effect of the CDE on lithium induced head-twitches, a serotonin mediated behavior was investigated. Lithium sulphate administered to animals releases serotonin from serotonergic neurons which stimulate the 5-HT_2 receptors and produced head twitches. These head twitches are antagonized by drugs that block 5-HT_2 receptors[10]. In the current investigation, pretreatment with CDE (25, 50 and 75 mg kg^{-1}) significantly reduced number of lithium induced head twitches. This concludes that CDE act as 5-HT_2 antagonist.

Thus, it may be concluded that dual protective effect of CDE in epilepsy and depression is associated with diverse mechanism namely GABAmimetic and 5-HT_2 antagonistic action.

Interestingly, vitexin, a flavone C-glycoside has been reported to have various effects related to the Central Nervous System (CNS), including anticonvulsant[35] and antidepressant activity[36]. Qualitative analysis of CDE revealed presence of flavonoids, steroids, glycosides and

alkaloids. Thus, it may be concluded that dual protective effect of CDE in epilepsy and depression may be due to the synergistic action of flavonoids and alkaloids present in *Cynodon dactylon*.

CONCLUSION

In present study, antidepressant activity of ethanolic extract of C. *dactylon* using reserpine induced hypothermia and forced swim test as well as antiepileptic activity using maximal electroshock induced convulsion and pentylenetetrazole induced convulsion was evaluated. The results of the present study showed that ethanolic extract of *C. dactylon* possess promising antidepressant as well as antiepileptic activity. From the mechanistic study performed using baclofen induced catatonia and lithium induced head twitch model, it was demonstrated that the antiepileptic effect of *C. dactylon* may be mediated through its GABAmimetic action and antidepressant activity may be mediated through 5 HT_2 antagonistic action (like atypical antidepressants). Thus, it may be concluded that dual protective effect of *C. dactylon* in epilepsy and depression is associated with diverse mechanism namely GABAmimetic and 5-HT_2 antagonistic action.

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