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Original Research Article

The antipsychotic activity of alcoholic extract of *Withania coagulans* fruits in Swiss albino mice

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ABSTRACT

Background: Schizophrenia is one of the most distressing central nervous system (CNS) disorders. It is described by positive, negative and cognitive symptoms. These symptoms can be controlled by the antipsychotic medicines. The numerous antipsychotic medications used today are not lacking the adverse drug reactions. The *Withania coagulans* a susceptible species, is not explored much for its CNS effects except in late seventies. Therefore, it was thought worthwhile to investigate anti-psychotic activities of alcoholic extract of *Withania coagulans* fruits. The objective of the present study was to assess the antipsychotic activity of alcoholic extract of *Withania coagulans* fruits in Swiss albino mice by Cook's Pole Climb Apparatus for conditioned avoidance response (CAR)

Methods: Cook's Pole Climb Apparatus for conditioned avoidance response was used for assessing the antipsychotic activity of the alcoholic extract of 200mg/kg, 500mg/kg and 1000mg/kg doses of *Withania coagulans* fruits.

Results: There was statistically (p-value >0.05) no significant association between any of the 200mg/kg, 500mg/kg and 1000mg/kg doses of the alcoholic extracts of *Withania coagulans* fruits with antipsychotic activity in Swiss albino mice.

Conclusions: Withania coagulans fruits alcoholic extract did not demonstrate antipsychotic activity in Swiss albino mice under standard conditions.

Keywords: Antipsychotic, Alcoholic extract, Conditioned avoidance response (CAR), Fruits, Swiss albino mice, *Withania coagulans*

INTRODUCTION

Schizophrenia is one of the most distressing central nervous system (CNS) disorders. The phenotype in schizophrenia is hard to outline because patients with this disease suffer from a widespread range of symptoms. The symptoms like deficiency of speech, deprived attention span, dull affect and want of motivation may live for lengthy periods of time. Such symptoms are named negative symptoms since they mirror the lack of common interpersonal and social functions. The more evident and flamboyant symptoms with strange manners and conducts during an extreme psychotic period are called positive symptoms like delusions and hallucinations.[1] A third cluster of symptoms encompasses shortages in cognitive functions, viz. dissociative thought disorders, tangentially, inarticulateness, looseness of associations, and impaired attention or information handling.[2]

There are numerous antipsychotic remedies available for the cure of schizophrenia. Yet, these medications cause Parkinsonism like adverse drug reactions in human.[3] The conditioned avoidance response (CAR) is considered for

antipsychotic screening. This is tested by Cook's Pole Climb Avoidance (CPCA). This test was developed by Cook and Catania in 1964 based on the conditioned avoidance and escape response.[4] The Conditioned Avoidance Response (CAR) model has been used since fifties. It has been found to have high predictive validity for detecting potential antipsychotic activity of drugs. The local application of a selective DA D2 antagonist suggested that suppression of CAR is mediated primarily by the inhibition of the mesolimbic, dopaminergic pathway which innervates structures such as the NAC, which also is in the line with notion of a dopaminergic over reactivity, especially in this region, being responsible for psychotic (positive) symptoms.[5] Furthermore, it was recently shown that antipsychotic like suppression of CAR by antipsychotic drugs begins to occur at the same drug striatal D2 occupancy levels (65-70%) i.e. usually needed for therapeutic response to antipsychotic treatment in schizophrenic patients.[6]

Withania coagulans is an exceptional species. This plant is principally used for the milk coagulation.[7] It is rarely found and so it is considered as 'vulnerable species'.[8] Fruits of this plant are used to control Diabetes Mellitus. The fruits are soaked in water for the whole night. After sieving the fruits the water so collected, drunk by the diabetic patient for about a month is very effective to control the blood sugar level.[7] Furthermore, they are useful in the chronic complaints of liver, dyspepsia, flatulent colic.[7] Moreover, they also act as sedative, alterative, emetic and diuretic.[7] Although a lot of work is done for its antidiabetic activity, not considerable work is executed on this plant to see the influence on the brain. In 1977 Budhiraja et al, reported central nervous system (CNS) depressant activity of this plant.[9] Afterward this plant was not at all explored for the CNS activity, though plenty of work was completed on Diabetes and other diseases. Therefore, it was thought valuable to scrutinize anti-psychotic activities of *Withania coagulans* fruits alcoholic extract.

METHODS

Apparatus

Cook's Pole Climbing Apparatus consisted of an experimental chamber with floor-grid in a sound proof enclosure. The enclosure had a sliding door of dull-faced clear acrylic Perspex plastic for viewing the activity of the mice. The right-hand side comprised of the electronic controls which provided both types of stimuli viz. audible or electrical, which might be presented singly or simultaneously through control buttons. These buttons could be manipulated through a timer for approximately 30 seconds which could be terminated any time before 30 seconds. The magnitude of voltage in Cooke's Pole Climb apparatus was designed for the study of behavioral effects of antipsychotic agents on small animals like rat or mice. The pole was in two portions screwed in the small lid on the top of experimental chamber. The smaller portion worked as a handle and longer one served as a pole which hanged inside the experimental chamber. Also raising the front sliding door upwards allowed an animal to be introduced into or removed from the chamber. A sliding tray was provided beneath the floor grip, which could be pulled out for cleaning.[10]

Procedure

A group of approximately 100 mice were trained to provide a colony for experimental study. From this colony, authors used 8 mice in each group to get better results.[11] Every mouse in turn, was placed in the test chamber for a period of 30 seconds without any stimulus, to allow and accommodate to the situation. If it climbed the pole, it was placed back in the grid floor where it should remain. Then a series of shocks were delivered to the stainless-steel grid floor continuously for 30 seconds or until the mice climbed to the safety area (Pole). After 2 or 3 exposures to this situation, they learned to climb the pole in respect to the buzzer only. When the latter response occurred on a stable basis, a conditioned avoidance response (CAR) is considered having developed. Prior to each experiment the CAR is reinforced a few times with the shock to increase the stability of the CAR throughout the day.

Control, standard and test drugs

Distilled water was given as vehicle for control. Injection haloperidol 0.1mg/kg s.c. was used as the standard drug.[12] The animals were treated 30min before the experiment with the test drugs (WCFAlcE of 200mg/kg, 500mg/kg and 1000mg/kg doses p. o.). However, the test drug was given every day for 30days throughout the period of experiment. Recordings were done on Day 1, Day 15 and Day 30 for all the groups. The recordings were taken half an hour after drug administration to the respective group.

Drugs were given in the following manner

Control: Vehicle (Distilled Water) 2ml/kg p. o. once a day for 30 days.

Standard: Standard Drug (Haloperidol) 0.1mg/kg s.c. half an hour before test.

- ALC-200: WCFAlcE 200mg/kg p. o. once a day for 30 days
- ALC-500: WCFAlcE 500mg/kg p. o. once a day for 30 days
- ALC-1000: WCFAlcE 1000mg/kg p. o. once a day for 30 days

Where WCFAlcE=Withania coagulans fruits alcoholic extract

RESULTS

As illustrated in Table 1, blockage of CAR decreased steadily for Alc-200. It was 50% on day 1st, 37.5% on day

15th and 25% on day 30th. It was 37.5% blockage on day 1st, 15th and 30th for Alc-500 dose. It means there was no change for the same for Alc-500. It was 50% blockage on Day 1 and 15th for Alc-1000. However, the blockage of CAR decreased to 37.5% on 30th day for Alc-1000. There were no significant differences in the blockage of CAR by any of the 200mg/kg, 500mg/kg and 1000mg/kg body weight of WCFAlcE on days 1st, 15th and 30th compared to control. However, there was significant ($p < 0.001$) blockage of CAR by the standard drug haloperidol on days 15 and 30 compared to control. It was 50% on day 1st, 87.5% on day 15th and 100% on day 30th. It means standard drug haloperidol showed increasing trend in the blockage of conditioned avoidance response which was statistically significant as well. Control showed 37.5% blockage on day 1st, 15th and 30th. From these results it is obvious that our test drugs did not showed more than 50% of blockage. There was no increasing trend observed with any of the ALC-200, 500 and 1000 doses. However, instead of increasing, the test dose ALC-200 showed decreasing trend. It means none of the test doses have the antipsychotic activity. If they had the activity, they might show increasing trend in the blockage of conditioned avoidance response. This might be statistically significant as that of the standard drug haloperidol. Since, blockage of CAR is attributed to the blockage of dopamine receptors mostly D2. It means present test drug *Withania coagulans* alcoholic extract does not have any activity on the Dopamine receptors. In contrast the standard drug haloperidol known to block the dopamine receptor. Therefore, it is proven drug for the antipsychotic activity.

Table 1: Effect of oral administration of WCFAlcE on blockage of CAR in mice (n = 8 in each group).

Group	Control	Standard	ALC-200	ALC-500	ALC-1000
Blockage of CAR day 1	37.50%	50%	50%	37.50%	50%
Blockage of CAR day 15	37.50%	87.50%***	37.50%	37.50%	50%
Blockage of CAR day 30	37.50%	100%***	25%	37.50%	37.50%

*p <0.05, **p <0.01 and ***p <0.001 when compared to control group; CAR: Conditioned Avoidance Response. WCFAlcE: *Withania coagulans* fruits alcoholic extract. Control: Vehicle (Distilled Water) 2 ml/kg p. o. once a day for 30 days. Standard: Standard Drug (Haloperidol) 0.1mg/kg s.c. half an hour before test. ALC-200: WCFAlcE 200mg/kg body weight p. o. once a day for 30 days. ALC -500: WCFAlcE 500mg/kg body weight p. o. once a day for 30 days. ALC -1000: WCFAlcE 1000mg/kg body weight p. o. once a day for 30 days.

The initial serum creatinine value before undergoing surgery were 0.87mg/dL and 0.86mg/dL with a standard deviation of 0.172 and 0.184 in AM and GM group respectively.

DISCUSSION

The central nervous system drugs, such as antipsychotics, opioid analgesics, and antidepressants, prevent conditioned avoidance responses (CARs) at doses that do not hamper escape responses (ERs).[13-15] On the other hand, other CNS depressants, such as benzodiazepines and barbiturate, block CARs in a nonspecific way. They disrupt CARs and ERs at approximately the same dose level.[16] Conditioned Avoidance Response (CAR) is a dopaminergic arbitrated reaction. Blocking of this reaction is endorsed to antagonism of postsynaptic dopaminergic receptors in nigrostriatal and mesolimbic dopaminergic systems as verified by the fact that haloperidol, a dopamine receptor opponent blocks the CAR learning.[17] This test was used in the screening of antipsychotic agents as phenothiazines block them.

As elucidated from Table 1, present study did not demonstrate the blockage of conditioned avoidance response (CAR) for the *Withania coagulans* fruits alcoholic extract (WCFAlcE) as the effects were not statistically dissimilar from that of the control. From the Cook's Pole Climb Apparatus (CPCA), it is obvious that WCFAlcE did not display the antipsychotic activity. It is clear that they might not act on the dopaminergic receptors. Yet, the thorough mechanism of action of these test drugs is still a clandestine and more behavioural tests built on the mechanism of action needs to be done.

As very few scientific studies have been reported on the effect of *Withania coagulans* (WC), so authors had to rely on data available on *Withania coagulans* (WS) which belongs to the same genus. Authors have got no actions for antipsychotic activity which is difficult to explain based on the current studies including ours. As WC contains some withanolides like Coagulin, Coagulanolides, Withacoagulin, Coagulins B-S which are not present in WS can explain difference of action between two species of same genus.[18]

CONCLUSION

Alcoholic extract of *Withania coagulans* fruits did not exhibit antipsychotic activity in Swiss albino mice as measured on the Condition avoidance response (CAR) by Cook's Pole Climb Response Apparatus. Further studies are warranted based on the mechanism of action on the dopamine receptors. More studies are necessary based on mechanism of action of the serotonin and nor-epinephrine receptors.

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