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Hippocampal-Dependent Spatial Memory and Histoarchitectural Integrities of the CA Regions of Wistar Rats Following Administration of *Rauwolfia vomitoria* and Chlorpromazine

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ABSTRACT

Psychotic patients demonstrate poor spatial memory, ascribed to impaired hippocampal functions, and bodies of evidences have attributed cognitive impairments to the poor functional outcomes in psychosis management. The efficacy of chlorpromazine and *Rauwolfia vomitoria* on spatial memory performance and differential histoarchitecture of the hippocampi of adult Wistar rats was examined in this study. Twenty five adult male Wistar rats weighing between 200 - 230 g were randomly grouped to five (Normal, low and high dose chlorpromazine and low and high dose *R. vomitoria*) of five animals each. 2 ml of normal saline was given to Control animals daily, 5mg/kg of chlorpromazine was given as low dose, 10 mg/kg of chlorpromazine was given as moderate dose, 150 mg/kg of *R. vomitoria* was given as low dose and 300 mg/kg of *R. vomitoria* was given as high dose orally. All the medications were given daily for 21 days. A Y-maze apparatus was used to assess the spatial memory performance in the rats at days 14 and 21 of the experiment. All the animals were euthanized using 20 mg/kg of intramuscular ketamine, cardially perfused with 4% paraformaldehyde, the brains and the hippocampus removed for histological analysis. Results from this study show that *Rauwolfia* at 150 and 300 mg/kg improved the correct decision (right triplet alternation) and reduced wrong decision (wrong triplet alternation) in the treated rats at days 14 and 21 respectively with an unaltered hippocampal histoarchitecture. While chlorpromazine at 5 and 10 mg/kg induced an increased wrong decision (wrong triplet alternation) and reduced correct decision (right triplet alternation) across treatment periods and caused an apparent distortion in the hippocampus. In conclusion, *R. vomitoria* could be a better alternative agent with more therapeutic potential in the treatment of psychosis and could possibly remediate cognitive impairments in psychosis.

Keywords: *Rauwolfia vomitoria,* chlorpromazine, psychosis, Hippocampal based spatial memory, Caudate Ammonis

INTRODUCTION

Impaired cognition is a common condition associated with the onset of psychotic syndrome (Salokangas and McGlashan 2008) and the cognitive outcomes of psychosis (Green 2006). Several complications like, verbal, executive, attention and memory deficits have been reported at the first episode of psychosis (Addington et al. 2006; Doughty and Done 2009; Leeson et al. 2009) and observed at all stages of the disease is abnormalities in working memory (Joyce et al.

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2002; Pantelis et al. 2009), while, progressiveness in cognitive flexibility is noticed during the course of the illness (Pantelis et al. 2009).

Psychosis has been associated with abnormal hippocampal functions evidenced extensively. These include, reduced hippocampal volume (Honea et al. 2005; Steen et al. 2006), increased hippocampal perfusion (Tamminga et al. 1992; Malaspina et al. 2004), reductions in the activation of hippocampal associated tasks (Eyler et al. 2003; Jessen et al. 2003) and impaired performance on hippocampal-dependent memory tasks (Titone et al. 2004; Ongür et al. 2006).

Antipsychotics are the common treatment for psychotic disorders and are found effective in the treatment of delusion and hallucination, which are the positive symptoms of the illness, but lack the efficacy on psychotic related cognitive impairments (Purdon et al. 2000; Keefe et al. 2004; Remington et al. 2010). The most common assumption would be that antipsychotic medications have no effects on hippocampal integrity and hippocampi associated functions in psychosis (Goldberg and Weinberger 1996), because of the paucity of documented data on the effects of antipsychotics on cognitive functions (Geyer and Tamminga 2004). But, studies have shown that antipsychotic drugs block D1 and D2 receptors in the hippocampus which are found majorly in CA1 and dentate gyrus leading to alteration in long term potentiation in the hippocampus (Matsumoto et al. 2008; Navakkode et al. 2007), thereby, modulating activity-dependent plasticity (Adams and Moghaddam 2001). It is thus necessary to research more to develop a novel antipsychotic with outright effectiveness and lesser burden of side effects.

Chlorpromazine (CPZ) is one of the first generation (typical) antipsychotics, commonly employed in the management of psychosis worldwide, but is usually associated with a lot of side effects (Adams and Moghaddam 2001). The major challenges facing the typical antipsychotics are their limitation in the exacerbation of adverse motor functions. However, the newer agents used, though have fewer side effects, they are relatively expensive and unavailable especially in the developing countries (Gardner et al. 1975; Miyamoto et al. 2005).

Rauwolfia vomitoria, a shrub plant, is found majorly in India, Malaysia, Thailand, Indonesia, Bangladesh and Burma. It also grows widely in the dense Africa forests and southern regions of Nigeria were it is locally called Ira-Igbo (Obembe et al. 1994). Its minimal side effects made it a common antipsychotic supplement in the traditional medical settings (Makanjuola 1987; Obembe et al. 1994). *Rauwolfia vomitoria* was nominated for this study, because of its widespread use in the management of psychosis in the developing nations and lack of adequate efficacy data, and concern regarding potential adverse effects, particularly on cognition.

Due to paucity of available data on the effects of oral administrations of chlorpromazine (CPZ) and *Rauwolfia vomitoria* (RV) on the hippocampal-l-dependent spatial memory and histoarchitecture integrities of the hippocampus and dentate gyrus. The present research compared the efficacies of *Rauwolfia vomitoria* with chlorpromazine on the hippocampal-dependent spatial memory and histoarchitecture integrities of the hippocampus and dentate gyrus, as cognitive domains and to suggest if *Rauwolfia vomitoria* could possibly remediate cognitive impairments in psychosis.

MATERIALS AND METHODS

Animals grouping

The experiment and procedure were approved by the University of Ilorin Animal Ethics Committee which parallel the National Institute of Health (NIH) guidelines on the use of animals in experimental research. Twenty five adult male Wistar rats weighing between 150 - 200 g were randomly grouped to five (control, low chlorpromazine, moderate chlorpromazine, low RV and High RV) of five animals each. The rats were caged in the mesh cages with proper feeding and under a natural light and dark rhythm, at room temperature and proper ventilation for a period of 14 days for acclimatization before commence of the experiment. 2 ml of normal saline was given to control animals, low chlorpromazine animals received 5 mg/kg of chlorpromazine, moderate chlorpromazine animals received 10 mg/kg of chlorpromazine, low RV animals received 150 mg/kg of *R. vomitoria* and high RV animals received 300 mg/kg of *R. vomitoria* orally. All the medications were given daily for 21 days. A Y-maze apparatus was used to assess the spatial memory performance in the rats at days 14 and 21 of the experiment. All the animals were euthanized using 20 mg/kg of intramuscular ketamine, cardially perfused with 4% paraformaldehyde and the brains were removed followed by the hippocampus for histological analysis.

Chlorpromazine and *Rauwolfia vomitoria* extraction and administration

Chlorpromazine hydroxide (Largactil) was purchased from a reputable government pharmacy in Ilorin, Nigeria. A tablet of Chlorpromazine (100mg) was dissolved in 40 ml of normal saline to produce 2.5mg/ml drug solution. The solution was administered to 5 and 10 mg/kg body weight of rats, using orogastric cannula. *R. vomitoria* leaves were obtained from the botanical garden of the University of Ilorin and authenticated by the record officer in the plant biology museum of the University. The leaves were washed, air dried, blended to fine substances. 100 g of the fine substance was dissolved in 1000 ml of distilled water, well shaken and left for 48 hours to dissolve properly. The mixture was filtered and the filtrate was evaporated to dryness in a water bath at 40 ºC. The resulting paste was weighed and dissolved in normal sa-

line (drive) and stored in the refrigerator until in use. 10 g from the paste was dissolved in 20 ml of normal saline. The extract solution was administered at 150 mg/kg.bw and 300 mg/kg.bw using orogastric cannula. The drug and extract solution were orally administered daily for 21 days.

Hippocampal-dependent spatial memory assessment

The behavioural test was conducted in a large quite room. Y-maze apparatus was used to assess the animals' spatial memory. A stop watch was used to score the behaviours and all events were observed manually. The Y-Maze experiments were done on days 14 and 21 of the administrations of chlorpromazine and *Rauwolfia vomitoria*.

A Y- maze is made up of three equally spaced arms, labelled as A, B, and C which are 120° from each other, 41 cm long and 15 cm high. It was used to assess the spontaneous alternation in the rats. The floor of the apparatus is 5 cm wide and is levelled with saw shaves. Each rat was stationed in one of the arms and allowed to freely explore the apparatus. The sequence or consecutive entrance of the animals into the arms is termed an alternation.

The total number of arms entered minus two is termed spontaneous alternations, and the percentage alternation was calculated as {(actual alternations /maximum alternations) × 100}". 10 minutes was assigned as the test time limit for each of the animals in the Y-maze apparatus. Recorded data include: (1) Right decision (correct triplet arm entries) which is defined as the respective accorded entry into the 3 arms at various times not entering a single arm repeatedly at two arms entry (e.g. ABCABCA, contain 5 correct triplet arms entries). (2) Wrong decision (wrong triplet arm entries), defined as repeated entrance into a specific arm, at just two interval of entering another arm or the same arm (e.g. ABCBCACA, contain 4 wrong triplet arm entries). And (3) Total arm entries indicate the total number of a single arm entered (e.g. ABCBCABACBC, contain 11 entries).

Animal sacrifice and Sample collection

At the end of the experiments, the animals were anaesthetized with intramuscular injection of 20mg/kg of ketamine, skin excised and transcardially perfused with 4% paraformaldehyde. The brains were removed and processed for histological analysis.

Statistical Analysis

Data from behavioural assessment were analysed using ANOVA followed by "Bonferroni's Multiple Comparison Test". Any value less than 0.05 was considered statistically significant and means ± SEM were the measure of presenting the data.

RESULTS

The result from the present study shows no significant (P<0.05) difference in the measure of the hippocampal-dependent spatial memory tasks (percentage alternations) assessment tests across all experimental groups (low chlorpromazine (5mg/kg), moderate chlorpromazine (10 mg/kg), low RV (150 mg/kg) and high RV (300 mg/kg)) when compared with the control (Figure 1). Although, there is no significant different in the measure of spatial memory (percentage alternation), the low chlorpromazine (5 mg/kg) and moderate dose (10 mg/kg) of chlorpromazine caused an up cline in wrong decision with average wrong triplet alternation of 3.80 ± 1.07 and 3.40 ± 1.03 respectively when compared with the *Rauwolfia vomitoria* 150 mg/kg (1.60 ± 0.60), 300 mg/kg (1.60 ± 0.51) and saline (0.60 ± 0.40) treated animals at day 14. While a more worsened wrong decision with average wrong triplet alternation of 5.60 ± 0.98 was recorded in the 5 mg/kg chlorpromazine treated animals at day 21. This indicated a dose and period of administration dependent deteriorating effects of chlorpromazine.

Rauwolfia vomitoria at 150 and 300 mg/kg significantly improved correct decisions in the treated animals over time and comparably higher to the chlorpromazine and saline treated animals. *Rauwolfia vomitoria*, caused an up increase in the correct decision with average right triplet alternation

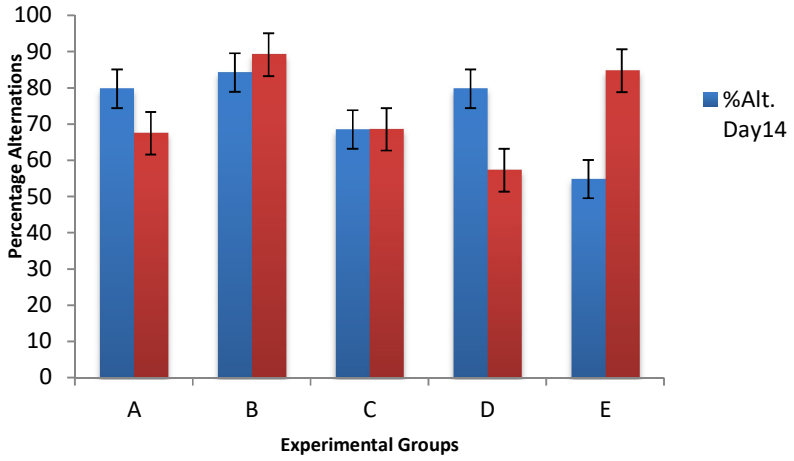

Figure 1: Effects of CPZ and *R. vomitoria* hippocampal-dependent spatial memory task showing the percentage alternations of the rats given saline (A), 150 mg/kg.bw of *Rauwolfia vomitoria* (B), 300 mg/kg.bw of *Rauwolfia vomitoria* (C), 5 mg/kg.bw of chlorpromazine (D) and 10 mg/kg.bw of chlorpromazine (E) in the Y-maze tests for 10 mins at days 14 (blue) and 21 (red). There was no statistical significance difference in the percentage alternations of all the animals at P<0.05, using ANOVA. Data are presented in means ± SEM.

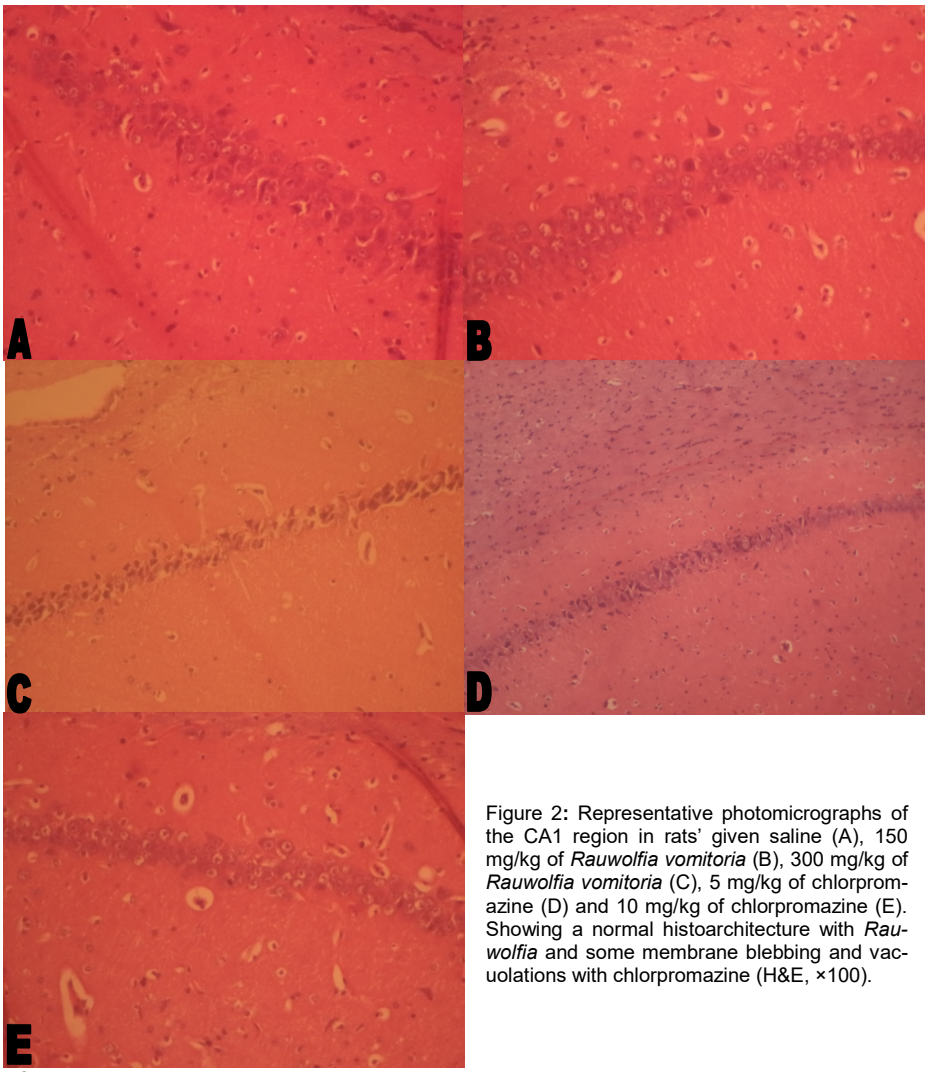

Figure 2: Representative photomicrographs of the CA1 region in rats' given saline (A), 150 mg/kg of *Rauwolfia vomitoria* (B), 300 mg/kg of *Rauwolfia vomitoria* (C), 5 mg/kg of chlorpromazine (D) and 10 mg/kg of chlorpromazine (E). Showing a normal histoarchitecture with *Rauwolfia* and some membrane blebbing and vacuolations with chlorpromazine (H&E, ×100).

of 8.80 ± 1.16 and 9.20 ± 2.39 respectively at day 14 and improved correct decisions with average right triplet alternations of 13.40±1.21 and 9.60±2.42 respectively at day 21. While chlorpromazine at both low and high dose caused a decline in the correct decision with average right triplet alternation of 13.80 ± 1.32 and 7.20 ± 0.37 respectively at day 14 and a more reduced correct decision with average right triplet alternations of 7.20 ± 1.91 and 6.00 ± 0.71 respectively at day 21.

The histoarchitectural observations of the histomorphology of the pyramidal neurons in the CA1, CA2 and CA3 regions of the hippocampus of the rats were normal in the control and *R. vomitoria* (150 and 300 mg/kg) administered rats, but appeared distorted in shape in the CPZ (5 and 10 mg/kg) administered groups. Some membrane blebbing were observed around the soma, in what appears like necrosis, but there were no necrotic cells observed (Figure 4).

DISCUSSION

Learning potentials and memory capacities during rehabilitation in psychosis is an important device used to assess the patients' functional outcome over a long period of time. However, there is poor understanding of the effects of antipsychotics on cognitive functions in psychosis, especially after a long time administration (Alvin et al. 2008). Deficit in spatial memory is one of the cognitive impairments that have been consistently associated with psychosis (Park and Holzman 1992; Keefe et al. 1995).

The main challenge today in the significant management of psychotic disorders are in the restriction of cognitive functions among the sufferers in which most available drugs in circulation including chlorpromazine, have failed to adequately address (Green et al. 2000). The study examined the comparative efficacy of *Rauwolfia vomitoria* and chlorpromazine on the hippocampal-dependent spatial memory and histoarchitectural integrities of the hippocampus and dentate gyrus, as cognitive domains, to suggest if *Rauwolfia vomitoria* could possibly remediate cognitive impairments in psychosis and psychosis treatment.

Hippocampal-dependent Spatial Memory

Spatial working memory performance is also of interest in the evaluation of medications because it is altered by drugs commonly used in the treatment of schizophrenia. The repeated acquisition approach (14th and 21st days) to Y-maze test was to evaluate the learning and retrieval efficacies of *Rauwolfia vomitoria* and chlorpromazine. This is more so, because, the animals' performance in the Y-maze test strongly depend on "spatial working memory" (Olton et al. 1976), mostly disrupted across various assessment procedures in psychotic individuals (Park and Holzman 1992; Keefe et al. 1995). Sergi et al. reported that acquisition ability of psychotic patients suggest their work skill potentials which is a determinant of the rehabilitation outcome (Sergi et al. 2007).

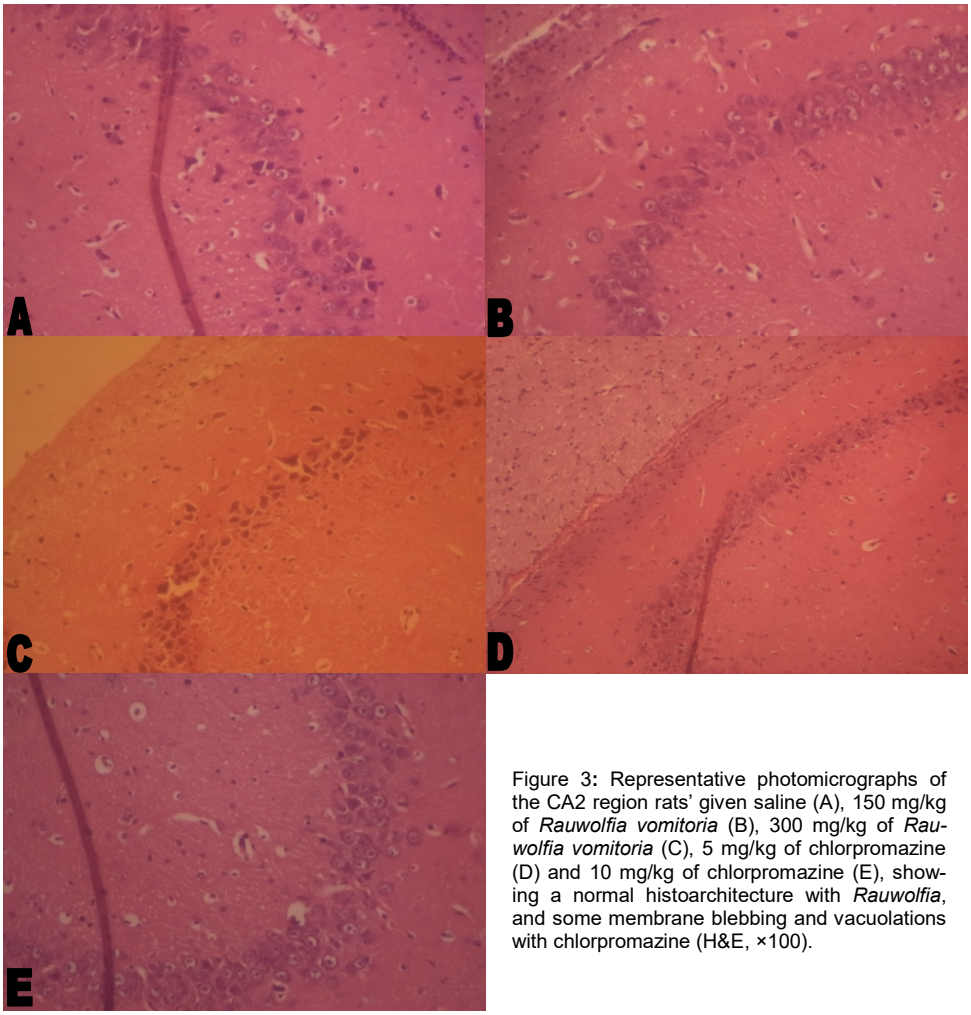

Figure 3: Representative photomicrographs of the CA2 region rats' given saline (A), 150 mg/kg of *Rauwolfia vomitoria* (B), 300 mg/kg of *Rauwolfia vomitoria* (C), 5 mg/kg of chlorpromazine (D) and 10 mg/kg of chlorpromazine (E), showing a normal histoarchitecture with *Rauwolfia*, and some membrane blebbing and vacuolations with chlorpromazine (H&E, ×100).

The present study shows that chlorpromazine has no deteriorating effects on the hippocampal-dependent spatial memory measure (percentage alternation). This report is strengthened by past studies which suggested that antipsychotics have no deleterious effects on the spatial working memory of psychotic individuals (Park and Holzman 1992; Park and Holzman 1993; Park et al. 1995a; Park et al. 1995b; Carter et al. 1996). Although, others have reported an improved spatial memory with risperidol (McGurk et al. 2004), and an unaltered visual and verbal related working memory in patients treated with clozapine and olanzapine (Bilder et al. 2002; Rosengarten and Quartermain 2002).

Although chlorpromazine as reported from this study have no significant negative effect on the measure of hippocampal-dependent spatial memory (percentage alternation), it dose and time dependently caused an up cline in the wrong alternation decisions (wrong triplet arm entries) and a decline in the right alternation decisions (correct triplet arm entries) of the treated animals when compared with the *Rauwolfia vomitoria* treated animals and the saline treated animals (base line).

This is a pointer that chlorpromazine use though may have no deteriorating effect on hippocampal-dependent spatial memory, may dose dependently and progressively over time predispose users to memory deficits. This assumption is deduced from the declined correct decision and up thrust wrong decision observed in the chlorpromazine treated animals at days 14 and 21 respectively. And our assumption is strengthened by the work of Alvin et al. in 2008, where impaired memory retention was reported in chlorpromazine treatment. Also, haloperidol and clozapine have been reported to worsen spatial memory (McGurk et al. 2004) where such effects are suggested by impairment in visual memory (Goldberg and Weinberger 1994; Hoff et al. 1996) and verbal working memory (Hagger et al. 1993) during the treatments with the agents.

Although, *Rauwolfia vomitoria* does not from this study have any significant advantage in the measure of hippocampal-dependent memory (percentage alternation), from its relative positive effects on correct decisions and negative effects on wrong decisions when compared with the base line treatment (saline) and chlorpromazine treatment, it is suggested that *Rauwolfia vomitoria* could possibly remediate cognitive impairments in psychosis.

Histoarchitecture

Histomorphological observations of the pyramidal cells in the CA1, CA2 and CA3 areas of the hippocampus and some granular cells of rats show no morphological alterations with oral administrations of *R. vomitoria* and this is in contrary with the findings of Eluwa et al. (2009). While some malformations, like membrane blebbing are observed in the histomorphology of the pyramidal neurons in the hippocampus of the rats given chlorpromazine. This is earlier reported that altered cortical neurogenesis predispose to neuropsychiatry disorders (Shors et al. 2001; Oomen et al. 2010).

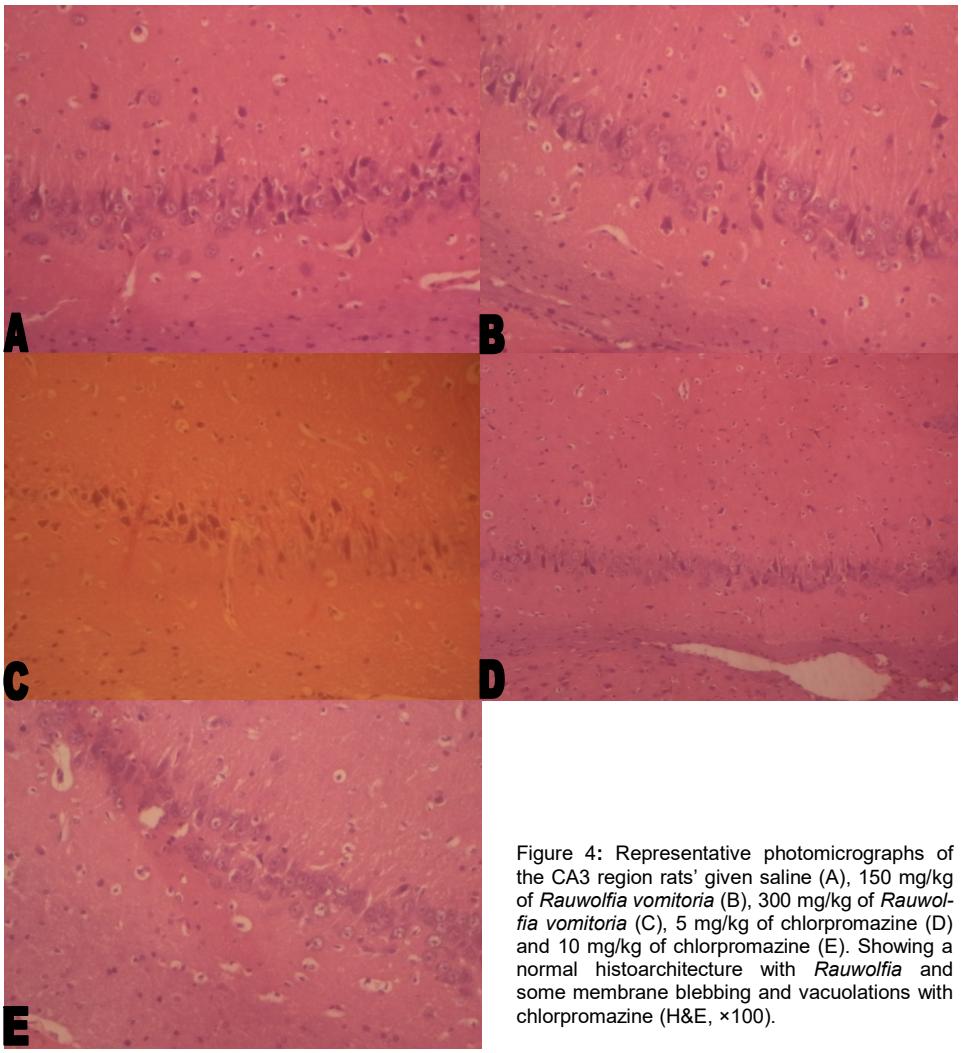

Figure 4: Representative photomicrographs of the CA3 region rats' given saline (A), 150 mg/kg of *Rauwolfia vomitoria* (B), 300 mg/kg of *Rauwolfia vomitoria* (C), 5 mg/kg of chlorpromazine (D) and 10 mg/kg of chlorpromazine (E). Showing a normal histoarchitecture with *Rauwolfia* and some membrane blebbing and vacuolations with chlorpromazine (H&E, ×100).

CONCLUSION

It can be concluded from the results of the present study, that chlorpromazine may have deleterious effects on spatial working memory in rats. This result suggest possible undesired effects of chlorpromazine on cognitive functions impairments (Terry and Mahadik 2007) and *R. vomitoria* could be a better complementary or supplementary therapeutic with memory enhancing efficacy and no deleterious effects on hippocampal-dependent spatial memory as impairment in cognitive related functions (Gur et al. 2002).

Conflict of interest
None declared

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