SJIF Impact Factor: 6.711

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 7.
Issue: 12
Page N. 241-247
Year: 2023

Original Article www.wjahr.com

COMPARATIVE EVALUATION OF SCHIZANDRA FRUIT AND VITAMIN E ON LEARNING AND MEMORY BEHAVIOUR IN EXPERIMENTAL MODEL OF STRESSED SWISS CDI MICE

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Received date: 21 October 2023 **Revised date:** 11 November 2023 **Accepted date:** 01 December 2023

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ABSTRACT

Schizandra fruit and vitamin E were evaluated for comparative cognitive health benefits in Swiss mice. Stress was induced in rodents pre-administered with schizandra and vitamin E, within experimentally designed scope. Thereafter, they were assessed alongside non-treated control rodents with Neurobehaviour parameters (swim latency, retention quadrant duration, annulus crossings, percentage % correct entry); that depict learning and memory, using established protocols of Morris water maze and spontaneous alternation test. From the observations, treatment with schizandra (referential) and vitamin E (known standard pill) both enhanced visuospatial memory in stressed mice, with vitamin E appearing more potent. Although isolated investigation of active ingredient in schizandra may be more hopeful.

KEYWORDS: Schizandra, Vitamin E, biological Stress, chemical stress, learning, memory.

INTRODUCTION

The quest to find out more affordable and relatively conveniently accessible methods of handling disorders which are associated with the nervous system is no doubt, garnering attention in the world of research (Landrigan 2012). And alongside this, is the long standing acceptability and patronage for traditional methodologies or remedies with huge reliance on medicinal plants (Manzano *et al*, 2020; Gurib-Fakim, 2006). To a large extent, this had been due to the limitations of exposure amongst the populace, particularly in developing countries and Africa. But this drive seems to have been reinforced even in the midst of awareness and new knowledge; particularly with cognizance of numerous negative side effects that modernized and orthodox medications have been reported to exhibit (WHO, 2002; Laurence *et al*, 1997).

In view of these, many researches on natural plants remedies are being carried out, and have continued to receive encouragement; although myriad of plants that are at the disposal of these populace, with acclaimed successful application as natural therapy do not have scientific bases yet (Karimi *et al*, 2015). The focus of some investigators has been to explore these natural herbs in experimental models for any possible therapeutic values (Sule *et al*, 2017a; Sule *et al*, 2017b).

It is reported widely that many plants have phytochemical constituents with bioactive properties; and further scientific exploration of this has been of benefit to pharmaceutical industries in the course of development of new and modern /orthodox medications with improved effectiveness (*Salmerón-Manzano et al*., 2020).

Schizandra is one of several plants mentioned for natural therapeutic claims, and acceptably used in Chinese clime for gastroenteritis, respiratory ailments and more (Nowak *et al*, 2019). But much needs to be reported about its scientific status, just as claims of its influence on central nervous system (Zhang *et al*, 2018). Some attributes have been accredited to this natural herb, which include adaptogenicity (Nowak *et al*, 2019).

It is in the light of these that schizandra was selected for investigation, peradventure it may portend any neurological health benefits; specifically to human learning and memory behavioural process that is largely affected adversely by neurodegenerative disease (Sandi, 2013).

METHODS

Standard established protocols in line with ethical approval for animal experimentation were followed. Swiss mice (C57BL/6) bred in animal house, University

of Calabar was used. It was in the design to use pups, therefore pregnant dams monitored in single cages till term were co-opted and their two days old pups (seventy-two in number) are randomly redistributed to groups (Grp) and administered as presented in design below; after acclimatization (Joffa *et al*, 2024).

Grp 1 had mice sub-grps 1(control), 2 (biologically stressed), and 3 (chemically stressed).
Grp 2 had mice sub-grps 1 (control), 2 (Vitamin E treated) and 3 (Schizandra treated).
Grp 3 had mice sub-grps 1 (control), 2 (Vitamin E treated) and 3 (Schizandra treated).
Grp 4 had mice sub-grps 1 (control), group 2 (Vitamin E treated) and 3 (Schizandra treated)

A biological method of stress induction, in line with model by Monteiro *et al*, 2015 was used with slight modification to achieve stress in the rodents, such that mice were daily isolated as social deprivation, exposed to 1 hour of sudden loud noise from generator, subjected to longer hours of light and 20 minutes of cold, in the experiment duration. Also, stress was induced using 3-nitropropionic acid which was administered to mice group at 15mg/kg intraperitonealy daily for 4 days (Binat *et al*, 2005).

The whole grps and sub-grps of mice were treated as designed from age - day 2; Sub-grps of control mice under grps 1 and 2 had normal mouse feed with water ad libitum, and controlled laboratory temperature / light exposure, but sub-grps of control mice in grps 3 and 4 were subjected to biological and chemical stress (Monterio *et al*, 2015; Bizat *et al*, 2005) in that order. Also, sub-grp 2 and 3 mice of group 1 was stressed biologically and chemically respectively, while sub-grps 2 and 3 mice of group 2 were given Vitamin E and Schizandra in that order without subjection to stress. However, all main grps 3 and 4 mice, were exposed to biological and chemical stress, but additionally, sub-grp 2 and 3 of main grp 3 were treated with Vitamin E and Schizandra in that order; in the way that sub-grp 2 and 3 of grp 4 were treated with Vitamin E and Schizandra.

The dosages were vitamin E (0.5mg/kg) and Schizandra (2mg/kg) once daily, as appropriate. On age – day 24, i.e. the day 22 of the experiment the animals were subjected to neurobehaviour tests adhering to established protocols of (Morris, 1984; Dao, 2010) as adopted by (Joffa *et al*, 2024; Erigbali *et al*, 2024) below:

Morris Water maze (MWM): This consists of circular plastic pool of water (at 28 ± 2˚C temperature) with established specification designed to study spatial learning and memory behaviour (Crawley, 2008); with four demarcated quadrants (Northeast - NE, Northwest - NW, Southeast -SE, Southwest - SW) made nontransparent with addition of non-harmful white paint. The standard method of Morris, 1984 as adopted by (Joffa *el al*, 2024) involving eight (8) days of acquisition, reversal, probe trial protocols was performed.

The T – Maze Test: The method of Dao, 2010 for one of the easiest among mazes, with two turns (left or right) at a top end farther from base of the T was applied. Here, any of the left or right paths may be barricaded as a way of alteration (Dao, 2010), while reward could be alternately placed on each side to see how the rodents would preferentially navigate previous arm that had reward as a measure of spatial memory (Dao, 2010).

Statistical Analysis
Standard statistical tools (ANOVA and LSD) were implored to analyze collated data, utilizing SPSS version 17.0 and recorded results (Mean ± SEM) were also displayed as bar charts (Joffa *el al*, 2024).

RESULTS
The results are as follows;

Comparison of percentage correct entry in the (T-maze) spontaneous alternation test for stressed and non-stressed mice
There was significant ($P<0.001$) decrease in the mean percentage correct entry for biologically stressed and chemically stressed groups of mice compared to control (figure 1)

Comparison of percentage correct entry in the spontaneous alternation test for non-stress mice administered schizandra (2mg/kg) ; vitamin E (0.5mg/kg)
In the non-stressed mice, the mean percentage correct entry was significantly ($P<0.05$) reduced for **schizandra** than vitamin E animals, but was not different compared to control. Meanwhile in vitamin E animals this increased than control, figure 2.

Comparison of percentage correct entry in the spontaneous alternation testing biologically-stress mice administered schizandra (2mg/kg) ; vitamin E (0.5mg/kg)
The mean percentage correct entry in this test with biologically-stressed mice was significantly ($P<0.001$) increased for **schizandra** and vitamin E treated groups compared to control, but there was no difference between schizandra and vitamin E group of mice, figure 3.

Comparison of percentage correct entry in the spontaneous alternation test for chemically-stress mice administered schizandra (2mg/kg) ; vitamin E (0.5mg/kg)
In this case with chemically-stressed mice, there was significant ($P<0.001$) increase in mean percentage correct entry in the spontaneous alternation test by both **schizandra** and vitamin E treated groups than the control, while schizandra had significantly decreased correct entry percentage than vitamin E (fig 4).

Swim latencies in MWM of non-stress animals administered schizandra (2mg/kg); vitamin E(0.5mg/kg) as shown in Learning curves
The swim latencies in Morris water maze as seen from the learning curves did not present any significant difference for the **schizandra** and vitamin E treated groups as well as control (P<0.05) fig 5.

Swim latencies from learning curves in MWM of biologically- stress animals administered schizandra (2mg/kg); vitamin E(0.5mg/kg)
Between all animals at acquisition training (fig 6), it was not different (P<0.05).

Learning curves showing swim latencies in Morris water maze test for chemically-stressed mice treated with schizandra (2mg/kg) and vitamin E(0.5mg/kg)
The indices investigated here showed no significant difference in the treated groups as well as control during all the acquisition training, see figure 7.

Quadrant durations in Morris water maze test showing preference for the NW (Reversal) quadrant in mice treated with schizandra (2mg/kg) and vitamin E (0.5mg/kg)
These indices revealed no difference between all groups as presented (figure 8). It is worth noting that there was no significant difference in the preference for NW (reversal) quadrant shown by all the categories; non-stressed mice treated with **schizandra** (2mg/kg) and vitamin E(0.5mg/kg); biologically-stressed mice treated with **schizandra** (2mg/kg) and vitamin E(0.5mg/kg).

Comparison of retention quadrant duration in non-stressed mice treated with schizandra (2mg/kg) and vitamin E(0.5mg/kg)
Mean retention quadrant duration was increased significantly (p<0.05) in vitamin E than schizandra treated group and significantly (p<0.01) in vit. E than control in non-stressed mice. In the schizandra group it was higher than control but not significantly (p<0.05), fig 9.

Comparison of retention quadrant duration in biologically-stressed mice treated with schizandra (2mg/kg) and vitamin E(0.5mg/kg)
In the biologically stressed mice treated with **schizandra** and vitamin E, during Morris water maze test, the retention quadrant duration increased significantly (p<0.05) in vitamin E than schizandra treated group and significantly (p<0.001) in vit. E than control. Also, this retention duration was significantly higher for s**chizandra** group than control at P<0.001 (fig 10).

Comparison of retention quadrant duration in chemically-stressed mice treated with schizandra (2mg/kg) and vitamin E(0.5mg/kg)
In this mice, observations of their mean duration in retention quadrant increased significantly (P<0.01, P<0.001) for both treated groups (**schizandra** and vitamin E) respectively when compared to control, while schizandra group had less duration than vitamin E mice which was not significant at P<0.01 (figure 11).

Comparing annulus reversal crossings for non-stressed mice treated with schizandra (2mg/kg); vitamin E(0.5mg/kg)
In the non-stressed mice, mean annulus crossings for schizandra treated mice was reduced compared to control and vitamin E groups, although this was not statistically significant (P<0.05). However, this elevated for vit. E significantly than control (fig 12).

Comparing annulus reversal crossings in biologically-stressed mice treated with schizandra (2mg/kg) and vitamin E(0.5mg/kg)
The annulus reversal crossing mean value in biologically stressed mice was increased significantly for schizandra group than control (p<0.001), and decreased significantly than vitamin E group (P<0.05). Meanwhile, it was significantly higher for vitamin E group than control at P<0.05 (fig 13).

Comparison of annulus reversal crossings in chemically-stressed mice treated with schizandra (2mg/kg) and vitamin E(0.5mg/kg)
Mean annulus reversal crossings in those chemically stressed mice were significantly (p<0.001) increased for both schizandra and vitamin E treated mice than control. The schizandra group had decreased reversal crossings than control which was not statistically significant (fig 14).

DISCUSSION

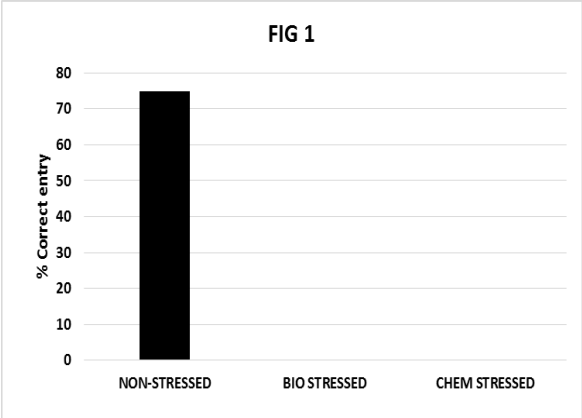
This research evaluated impact of schizandra fruit and vitamin E comparatively, on learning and memory behaviour of Albino Swiss mice that was induced with stress (Dokkaew *et al*, 2009) which can have deleterious impact on memory (Radi *et al*, 2014). Following stress induction, Vitamin E and schizandra pretreated rats were observed for parameters that assess learning and memory alongside non-treated control animals. From the results of the Morris water maze test, the learning curves during acquisition and reversal days shows all mice learned without impairment (Fig. 5,6,7). But at reversal trainings, when changing of escape platform location was done, schizandra and vitamin E administered animals learned quicker than the biologically and chemically stressed animals for days 1 and 2 reversal trainings, as illustrated by longer swim latencies recorded (fig 11).

When probe trial was performed to assess visuospatial memory in the animals, the stressed groups presented with Neurobehaviour parameters that implies they had impairment of visuospatial memory which was more severe in chemically stressed mice. However, the schizandra and vitamin E administered mice exhibited neurobehaviour parameters indicative of a reversal of visuospatial memory impairment or improved memory (fig 13,14).

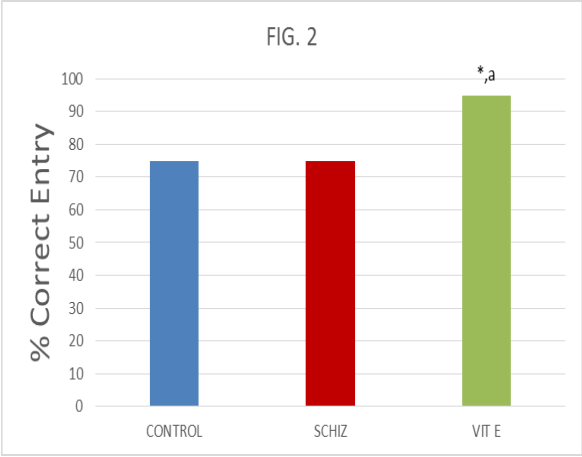
Furthermore, swim latencies was not different between the test groups and control in visible platform task, showing the animals all had normal visual cues with no visual impairment to interfere with them locating platform accurately. More so, results from spontaneous alternation test reveal that schizandra and vitamin E may have enhancing effect on working memory.

In Summary, it can be inferred from the observations that treatment with schizandra – reference herbal remedy and vitamin E – known standard (Rahangadale *et al*, 2012; Alzoubi *et al*, 2012) enhanced visuospatial memory in stressed mice. However, comparatively, the potency of vitamin E appears to be greater in those mice stressed biologically. But contrarily, the observation was not same with those mice stressed chemically, which is probably not unconnected to severity of 3-NP neurotoxin. Also, there may be further hope in sight if the active ingredient in schizandra is isolated and investigated for this health benefit.

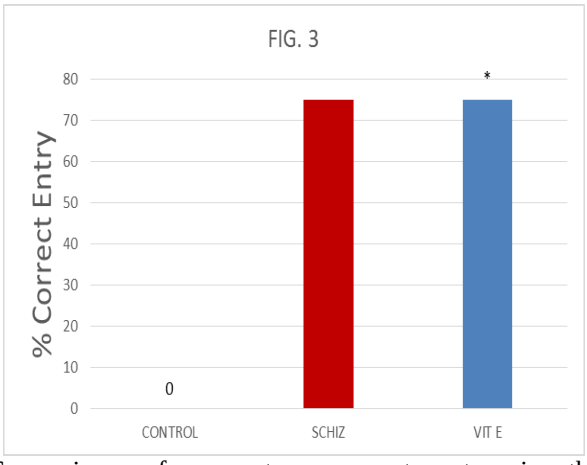
List of Figures



Comparison of percentage correct entry in the (T-maze) spontaneous alternation test for stressed and non-stressed mice, *** significant at p<0.001 vs control.



Comparison of percentage correct entry in the spontaneous alternation test for non-stressed mice treated with schizandra (2mg/kg) and vitamin E (0.5mg/kg): * = significant at p<0.05 vs control; a = significant at p<0.05 vs schizandra.



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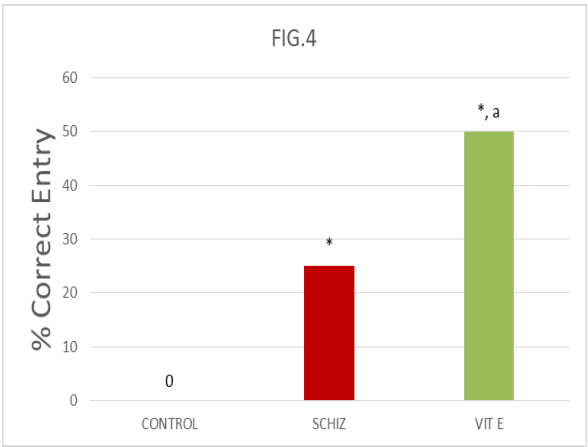

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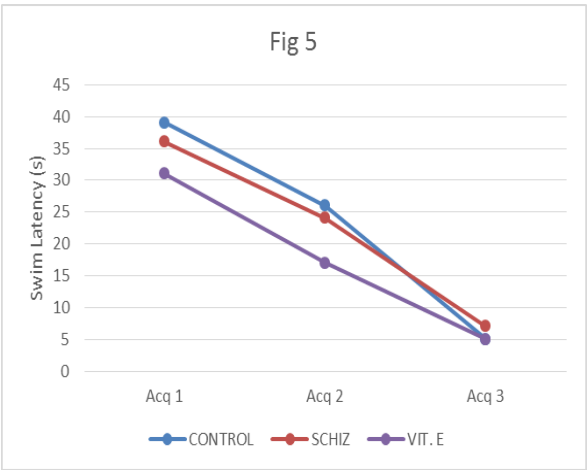
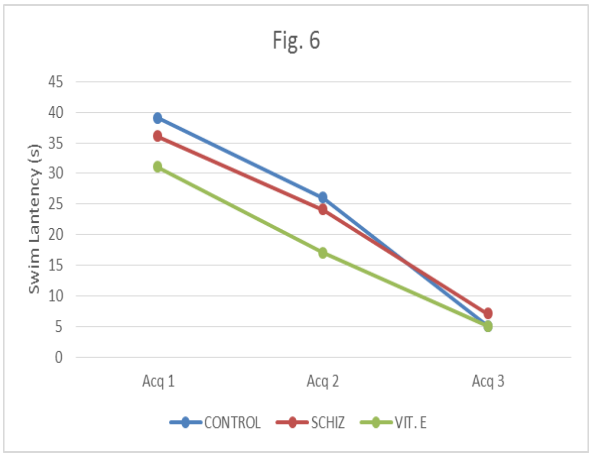
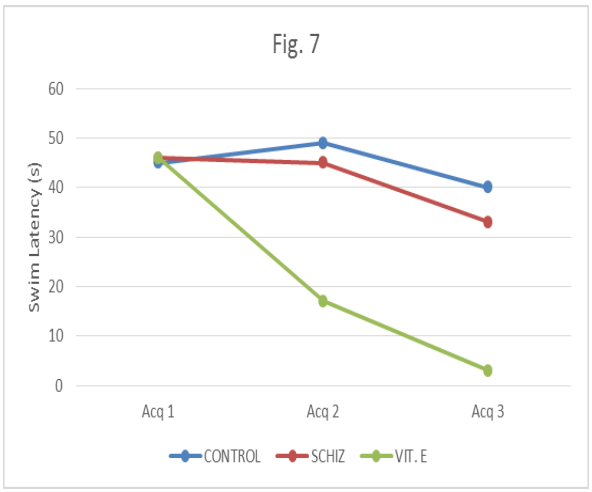


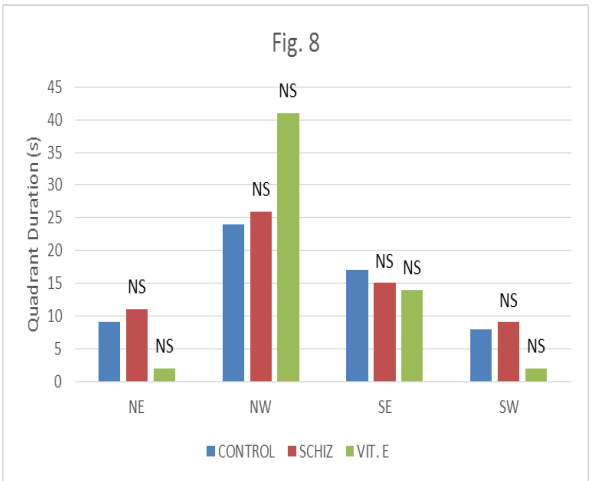
Swim latencies in Morris water maze test for non-stressed mice treated with scisandra (2mg/kg) and vitamin E (0.5mg/kg) as shown in Learning curves:



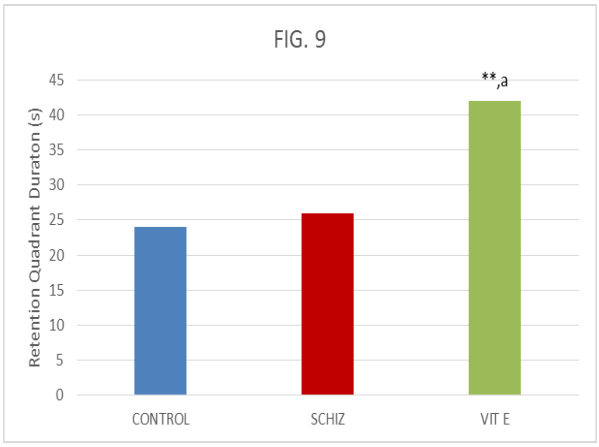
Swim latencies from learning curves in Morris water maze test for biologically- stressed mice (set 3) treated with schizandra (2mg/kg) and vitamin E(0.5mg/kg):



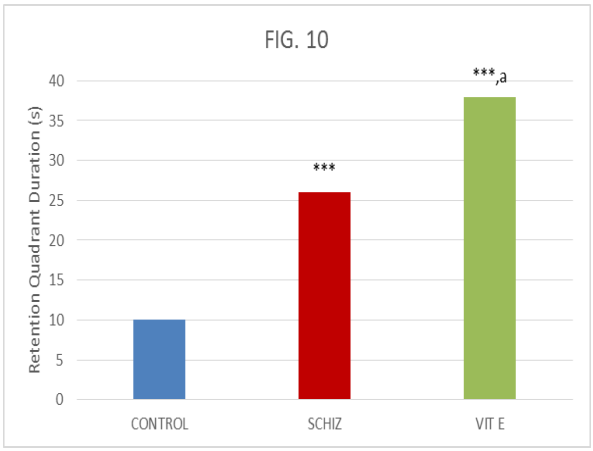
Learning curves showing swim latencies in Morris water maze test for chemically-stressed mice treated with schizandra (2mg/kg) and vitamin E(0.5mg/kg):



Quadrant durations in Morris water maze test showing preference for the NW (Reversal) quadrant in mice treated with schizandra (2mg/kg) and vitamin E (0.5mg/kg): NS= significant at p<0.05 vs control.



Comparison of retention quadrant duration in non-stressed mice treated with schizandra (2mg/kg) and vitamin E(0.5mg/kg): ** = significant at p<0.01 vs control ; a = significant at p<0.05 vs schizandra.



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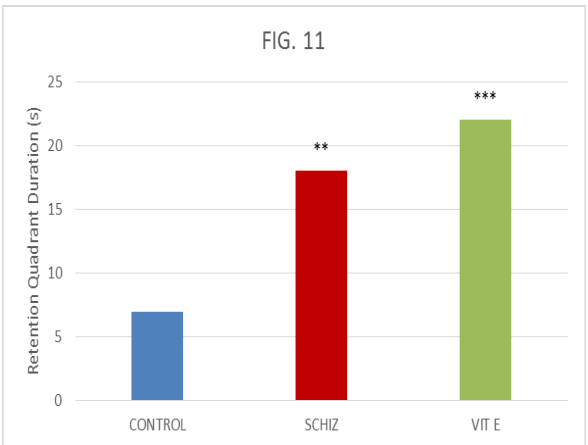

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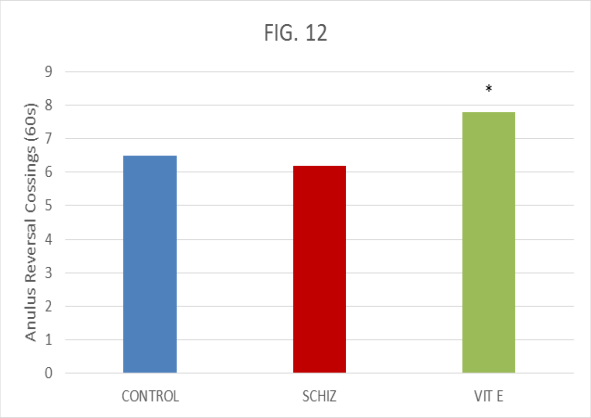
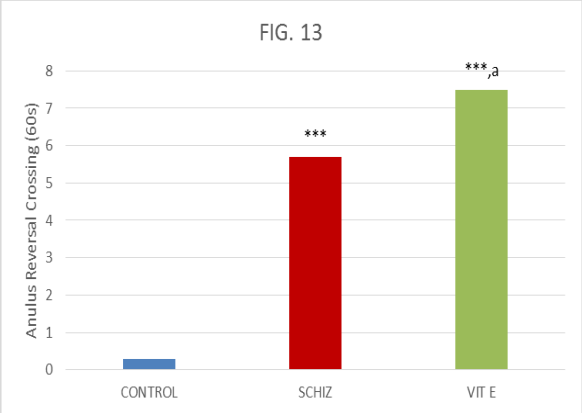
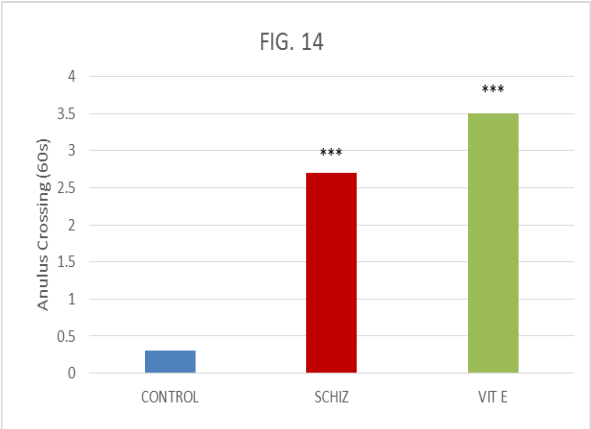


Comparison of annulus reversal crossings in non-stressed mice treated with schizandra (2mg/kg) and vitamin E(0.5mg/kg): *= significant at p<0.05 vs control.



Comparison of annulus reversal crossings in biologically-stressed mice treated with schizandra (2mg/kg) and vitamin E(0.5mg/kg): *** = significant at p<0.001 vs control; a = significant at p<0.05 vs schizandra.



Comparison of annulus reversal crossings in chemically-stressed mice treated with schizandra (2mg/kg) and vitamin E(0.5mg/kg): *** = significant at p<0.001 vs control.

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