Banana fruit pulp and peel involved in antianxiety and antidepressant effects while invigorate memory performance in male mice: Possible role of potential antioxidants

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Abstract: The present study was aimed to investigate the anti-stress and memory enhancing effects of banana (*Musa sapientum L.)* fruit pulp and peel extract in male mice. Locally bred albino Wistar mice were divided into control and 2 test groups (n=10). Control rats received drinking water while test groups were treated with banana fruit pulp (600 mg/kg; oral administration) and extract of banana peel (400mg/kg; oral administration). Behavioral activities of animals were monitored 14 days post administration of banana pulp and peel extract. Depression-like symptoms were measured by forced swimming test (FST). Anxiety like behavior was monitored using light-dark activity (LDA) test and plus maze activity (PMA) test and memory functions of rats were assessed by morris water maze (MWM) test. Following 2 weeks animals were decapitated and brain was removed for estimation of antioxidant enzymes such as catalase (CAT), super oxide dismutase (SOD) and reduced glutathione (GSH). In the present study both banana peel and pulp increased the time spent in light box and open arm, suggesting anxiolytic effects. A significant decrease in immobility time was observed in FST in both banana pulp and peel treated animals suggesting antidepressant like effects. Moreover, learning and memory assessed by MWM showed decrease in time to reach platform in both short term and long term memory test suggested increased memory function in both banana pulp and peel treated animals as compared to control animals. The activities of all antioxidant enzymes were significantly ($p<0.05$) greater in banana pulp and peel treated animals than control. It is concluded that both banana pulp and peel have anti-anxiety, antidepressant effect as well as strengthen the memory possibly via its antioxidant mechanism. Therefore, it is recommended that supplementation of banana could be taken a vital role in stress (anxiety and depression) relief and increased in memory function possibly by phyto-antioxidants.

Keywords: Banana pulp; banana peel; stress, depression; anxiety, antioxidant enzymes.

INTRODUCTION

The exploration of biologically active natural products haS played an important role in finding new chemical entities which has significantly contributed to the development of different traditional systems of medicine for the treatment of various diseases. This has extended to the discovery of different medicinal plants to find the scientific basis of their traditional uses (Jachak and Saklani, 2007). Although, challenges and opportunities in drug discovery from plants remain to be resolved, different parts of the banana plant are commonly used as food and medicine in many Asian countries (Joshi, 2000). Banana plant is known to be used in Indian folklore medicine and Ayurveda for the treatment of kidney stones, ulcers, skin diseases, gout, etc (Pellai and Aashan, 1955). Different parts of banana plant such as flower, pseudostem, rhizome, etc. have been studied for anti-ulcerogenic (Kumar *et al*. 2012) hypolipidemic (Dikshit *et al*. 2016), antimicrobial (Mangathayaru *et al*., 2004), antihypertensive (Anonymous, 2003), wound healing, antacid, diuretic and antiestrogenic activities (Jain *et al*., 2007).

Banana is known to be a good source of bioactive compounds such as dopamine, *N*-acetyl serotonin and polyphenols, etc., with high antioxidant properties (Dikshit *et al*., 2016). It contains different amino acids like threonine, tryptamine, tryptophan, flavonoids and sterols (Ivan, 2003). Several studies have revealed the hypoglycemic activity of banana (Dhanaba *et al*., 2005). Chloroform extract of *M. sapientum* flowers showed a reduction in blood glucose and glycosylated hemoglobin (HbA1C) levels (Pari and Maheshwari, 2000). It has also shown that the fruit peel ash of *M. sapientum* possesses acid neutralizing capacity and produced an increase in urine volume and K+ as well as other electrolyte excretion than normal saline in a study in rats. Moreover, an ethanolic extract of the same generated a diuretic effect (Jain *et al*., 2007). Evidence abounds in both folk medicine and experimental theories in the ability of banana and plantain to possibly reduce oxidative stress in

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vivo (Salau *et al*., 2010). A study illustrated significant reduction in oxidative stress after a single banana meal in healthy human due to its antioxidant activity (Salau *et al*., 2010).

Interestingly, *M. sapientum* also possesses antidiabetic, antidiarrhoeal, antidysentery and antihemorrhagic. Recent importance attributed to *M. sapientum* has gained the interest of scientists to investigate the medicinal importance of its different parts. Here we are examined the anti-stress and memory enhancing effects of banana pulp and peel, collected from local area of Multan, Punjab, Pakistan.

MATERIALS AND METHODS

Thirty male Albino Wistar mice weighing 20±2g purchased from University of Lahore, Lahore-Pakistan were used in the study. The animals were housed individually to avoid social interaction effect under a 12h light-dark cycle (light on at 6:00h) and controlled room temperature (22±2°C) with free access to cubes of standard rodent diet and tap water. Before starting experimental work, animals were subjected to 1 week of acclimation period and to various handling procedures in order to reduce the stress of novelty and handling. All experiments were carried out in a balanced design to avoid influence of order and time. All experiments were approved by Animal Resource Facility, University of Lahore, Lahore Pakistan, Institutional Ethical Committee and performed in strict accordance with National Institute of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985).

Plant material and preparation of extract

The fresh bananas were collected from the surrounding of Multan, Punjab, Pakistan and identified by the taxonomist as *Musa sapientum*. The extract of peel was prepared as described previously by Tee and Hassan (2011).

Treatment Schedule

Animals were randomly divided into three groups (n=10) and treated for 14 days respectively: (1) Control group (water treated) (2) Banana fruit pulp (paste; orally (600 mg/kg) (3) banana fruit peel extract (400 mg/kg; oral administration). Animals were treated with their respective treatment daily for 2 weeks from 0900 to 1300 h. After 2 weeks animals were subjected to behavioral analysis. Elevated plus maze (EPM) test and light dark activity (LDA) test were performed to measure anxiety. Forced swimming test was performed to determine depression. Morris water maze test was conducted to assess cognitive abilities. All experiments were carried out between 0900 and1600h. After the behavioral analysis animals were decapitated, brain and liver were removed and stored at -20ºC till the estimation of antioxidant enzymes (CAT, GSH and CAT).

Behavioral Analysis

Morris water Maze (MWM) test

Morris Water Maze (MWM) test was performed to examine the effects on spatial memory as described by Haider *et al.* (2012). We have assessed learning acquisition, the reference (long-term) memory and working (short-term) memory in terms of latency to locate the escape platform. The test is based on two phases: the training phase and the test phase. Memory functions of rats were tested by noting down the retention latency. The cut off time was 2 min for each session. Initially, the training session was performed during which each rat was placed into the water in such a way that their face was towards the wall of the tank. Each animal was given 120 sec to find and mount onto the hidden platform by using distal extra maze cues. Cues must be visible and useful to rats. They must be far enough to require the rat to use spatial analysis, rather than association, to solve the task. If the rat located the platform it was allowed to stay on it for 10 sec. Time on the platform must be sufficient for them to feel the location and to see the exact position. If it failed to locate the platform during the allocated time, then it was guided gently onto the platform. The test consisted of three trials: training, STM (short-term memory) and LTM (long-term memory). After training of animals STM was assessed 60 min after training session, and LTM was measured after 24 h of training.

Light-dark activity box (LDA) test

The test was conducted in a locally-made compartment box (Samad and Haleem, 2009). The compartment of equal size (26x26x26 cm), with an access (12x12cm) between the compartments, differed in their sensory properties. Walls of on compartment were light (transparent) and other dark (Black). A rat placed in this box expected to pass more time in the dark compartment. To determine the activity a rat was introduced via the dark compartment of the box. Time spent in the light compartment was monitored for a cut off time of 5 minutes.

Elevated plus maze (EPM) test

Anxiety was assessed by EPM according to the method as described by Naqvi *et al*. (2012). The apparatus used in the present study was consisted of two closed arms and two open arm s with same dimensions (50×10cm). Close arms were enclosed by 40cm high walls. The arms were connected with a central square (10×10cm) to give the apparatus a plus sign appearance. The maze was elevated 60 cm above the floor. To monitor the activity, rats were individually placed in the central square facing an enclosed arm and the time spent in open arm was recorded for 5 minutes.

Forced swimming test (FST)

The FST apparatus comprised of a glass tank with 56cm height and 30cm width, which contained water at the

height of 22cm and temperature of 25ºC. In this glass tank animals were individually forced to swim for 5min. The height of water was selected so that animal was prevented from touching the bottom of the glass tank and to prevent its escape from the glass tank. The FST is commonly used as standard pharmacological model for evaluating depression like symptoms in rats (Porsolt *et al*. 1981). When the rats are placed in an inescapable chamber which is filled with water then the development of the state of immobility reflects the cessation of persistent escape directed behavior. In this test animal's swimming behavior was monitored which can be defined as movement throughout the swim chamber (glass tank). The immobility time was monitored. The animal is considered immobile when it makes no further attempts to escape and only tries to keep its head above the water.

Biochemical estimation

Determination of Catalase (CAT) activity

Brain homogenate (10%) in 0.01M phosphate buffer (pH 7.0) was prepared and filtered. Then 0.1ml of filtrate was mixed with 1.4ml of reaction mixture that contained 0.4 ml of 2M hydrogen peroxide and 1ml of same phosphate buffer. The reaction was terminated after 1 min by adding 2.0ml of dichromate-acetic acid reagent. Blank contained distilled water in place of filtrate of brain homogenate. The absorbance of both test and blank were measured at 620 nm to calculate percent inhibition of CAT (Pari and Latha, 2004).

Determination of superoxide dismutase (SOD) activity

An aliquot of brain homogenate (10%) was treated with 0.75ml of ethanol and 0.15ml of ice chilled chloroform then centrifuged. Then 0.5ml of EDTA (0.6mM) and 1.0 ml of carbonate-bicarbonate (0.1M; pH 10.2) buffer was added in 0.5ml of supernatant. The reaction was started by adding 0.5ml of epinephrine (1.8mM) and the absorbance was measured for 3min at 480nm. Blank contained all reagents except supernatant. Finally, percent inhibition of SOD was calculated (Misra and Fridovich, 1972).

Determination of reduced glutathione (GSH)

0.5 ml of 10% brain homogenate and 2ml of 2% TCA (trichloro-acetic acid) were mixed and centrifuged. Then 1ml of supernatant allowed to reacts with 0.5ml of Ellman's reagent (19.8mg of 5, 5'-dithiobis-2-nitrobenzoic acid in 100 ml of 1% sodium citrate) and 3.0 ml of phosphate buffer (0.2M, pH 8.0). The absorbance was measured at 412 nm and percent inhibition was calculated (Ellman, 1959).

STATISTICAL ANALYSIS

The results are presented as mean ± SD for ten animals in each group. Data on behavioral (MWM, LDA, EPM and FST) and antioxidant enzyme (CAT, GSH and SOD) activities were analyzed by one-way (ANOVA). Post hoc analysis was performed by Tukey's test. P values<0.05 was taken as significant.

RESULT

Fig. 1 shows the time spent in the open arm of elevated plus maze in animals treated with banana pulp and peel. Data analyzed by one-way ANOVA showed significant ($F_{2,27}$=13.45 P<0.05) difference between control and test (Banana pulp and peel) groups. Tukey's test showed that time spent in open arm was increased in both banana pulp and peel treated animals than control.

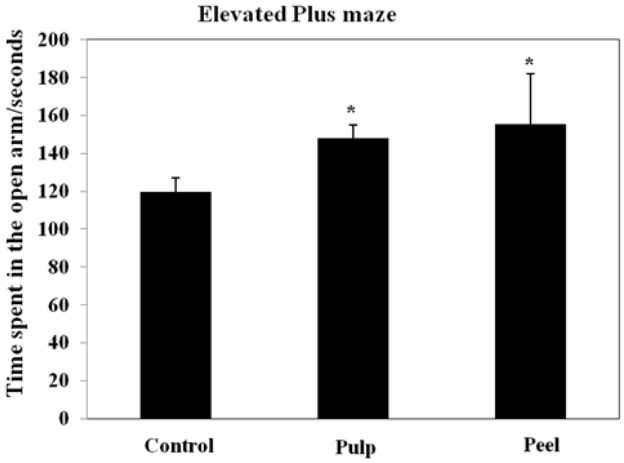

Fig. 1: Time spent in open arm in animals treated with Banana pulp and peel. Values are mean ± S.D. (n=10). Significant differences by Tukey's test: *P<0.05 from control animals following One way ANOVA.

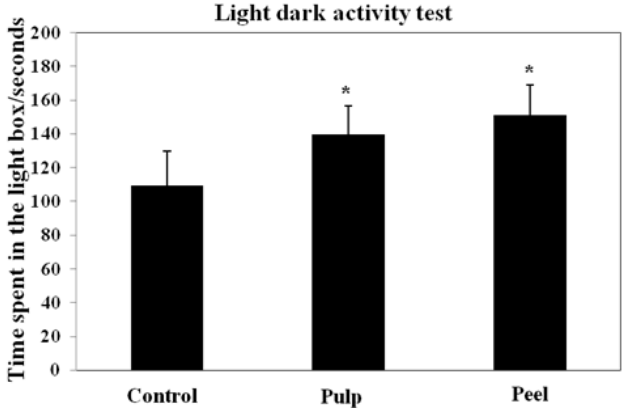

Fig. 2: Time spent in light box in animals treated with Banana pulp and peel.. Values are mean ± S.D. (n=10). Significant differences by Tukey's test: *P<0.05 from control animals following One way ANOVA

Fig. 2 shows time spent in light compartment in light dark activity box in animals treated with banana pulp and peel. Data analyzed by one-way ANOVA showed significant ($F_{2,27}$=13.85 P<0.05) difference between control and test (Banana pulp and peel) groups. Tukey's test showed that entries in light box were increased in both banana pulp and peel treated animals than control.

Fig. 3 shows immobility time in force swimming test in animals treated with banana fruit pulp and peel. Data

analyzed by one-way ANOVA showed significant ($F_{2,27}$=23.21 P<0.05) difference between control and test (Banana pulp and peel) groups. Tukey's test showed that immobility time was decreased in both banana pulp and peel treated animals than water treated control animals.

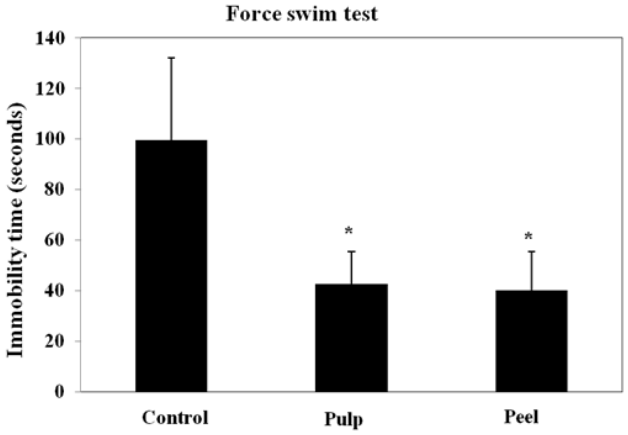

Fig. 3: Immobility time in force swimming test in animals treated with Banana pulp and peel. Values are mean ± S.D. (n=10). Significant differences by Tukey's test: *P<0.05 from control animals following One way ANOVA.

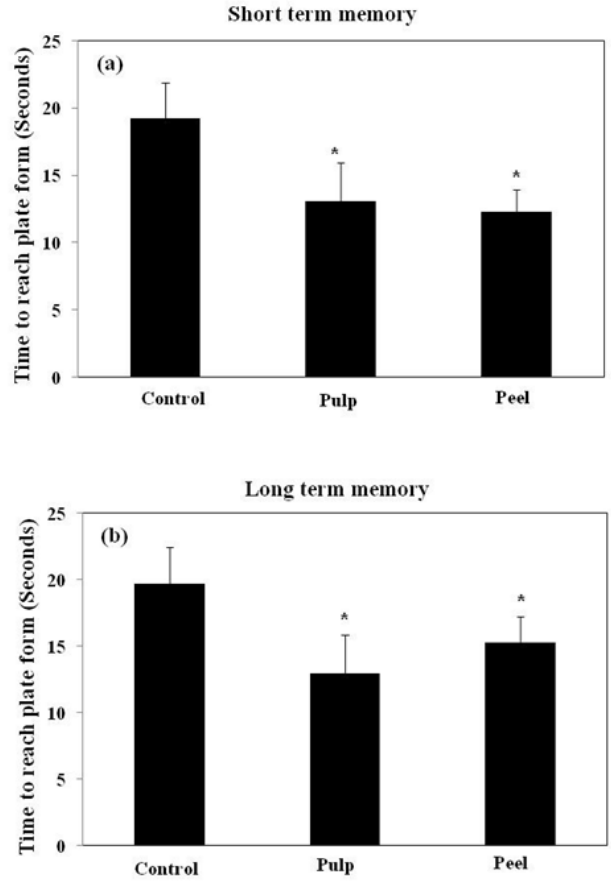

Fig. 4: Effect of Banana pulp and peel.on memory of mice. Values are mean ± S.D. (n=10). Significant differences by Tukey's test: *P<0.05 from control animals following One way ANOVA.

Fig. 4 shows MWM activity in vehicle, banana pulp and peel treated animals. The MWM activity is expressed as time to find the hidden platform performed after 1h (short term memory, fig. 4a) and after 24 h (long term memory, fig.4b). One way ANOVA for short term memory showed significant effect ($F_{2,27}$=24.91 p<0.05) of both tests. Long term memory was analyzed by one-way ANOVA showed significant effects ($F_{2,27}$=17.76 p<0.05). Tukey's test showed that pre-administration of banana pulp and peel enhance the memory and decreased the time to reach to hidden platform in after 1h of training suggesting increase STM. Banana pulp and peel also decreased the time to reach to hidden platform during 24 hrs time.

Table1 shows effects of banana pulp and peel on antioxidant enzyme (CAT, SOD, GSH) activities in brain and liver. One-way ANOVA showed overall significant (P<0.05) effect of banana pulp and peel on antioxidant enzyme in brain. Post-hoc analysis by Tukey's test showed that activities of CAT, GSH and SOD in the brain were significantly (P<0.05) increased in banana pulp and peel treated animals.

DISCUSSION

Plants are rich sources of nutraceuticals. Various plant extracts which are rich in bioactives are increasingly finding use in functional foods which are said to bring about health benefits. Among these plant-derived compounds are flavonoids which recently have attracted interest because of their biological activities to human health, also because of their influence on central nervous system effects (Fernandez *et al*., 2006). The influence of plant derived compound on anxiety (Joshi *et al*., 2005), depression (Bhutada *et al*., 2010), learning and memory processes (Nassiri-Asl *et al*., 2013) has been reported. Therefore, in the present study, we have hypothesized that banana pulp and peel extracts in male mice have antianxiety, antidepressant and memory enhancing effects via their possible antioxidant mechanism.

M. sapientum is a widely available plant in South East Asia which has been evaluated for its antioxidant properties in a few previous studies. One of these studies attributed the hepatoprotective quality of the plant extract to its antioxidative property. The study showed that the plant extract prevented rise in malondialdehyde (MDA) and increased glutathione (GSH, GPx) and SOD levels in treated group (Dikshit *et al*., 2011). Another study found decreased serum lipid peroxidation and increased serum SOD in diabetic rats treated with the plant extract (Adewoye *et al*., 2009). One more study found the antiulcerogenic activity of the plant extract to be related to its antioxidant activity (Goel *et al*., 2001).The natural cellular antioxidant enzymes include SOD, which hunt the

Table 1: Values are mean ± SD (n = 10). Data was analyzed by Tukey's test following one ANOVA. Statistical difference versus vehicle treated control groups.

	Control	Pulp	Peel	F-values
CAT (gm/dl)	0.115±0.01	0.149±0.03^{+}	0.168±0.03^{+}	7.75, p<0.05, df 2,27
GSH (%)	27.90±3.86	38.68±6.30^{+}	40.64±5.17^{+}	17.33, p<0.05, df 2,27
SOD (%)	85.12+4.65	94.45±3.93^{+}	93.07±4.28^{+}	13.71, p<0.05, df 2,27

+Statistical difference $p < 0.05$.

super oxide by acceleration its dismutation; CAT, a heme-containing enzyme which removes hydrogen peroxide (H_2O_2) and other peroxide, and GPx, a selenium-containing enzyme, which hunt H_2O_2 and other peroxides (Blake *et al*., 1987).

It has been stated that the stress response begins when the individual considers a situation as involving a threat, harm, loss or challenge. Immediate exposure to stress has been reported to induce anxiogenic behavior that may result in excitable and irritable state leading to impaired performance (McEwen and Wingfield, 2003). Exposure to the elevated plus-maze and light-dark activity test induces behavioral and physiological effects in rodents consistent with fear/anxiety (Rodgers *et al*., 1999). During such kind of stress episode an immediate response activates HPA axis and sympathetic nervous system that helps the organism to survive. In humans, as in other animals, these hormones help the body to deal with stressors with the normalization of antioxidants status (Haider *et al*., 2015).

Oxidative stress can be an important factor in the genesis of mood disorders such as anxiety and depression. Patients with depression have decreased antioxidant defenses and more oxidative DNA damage as compared to un-depressed individuals, and studies have found significantly increased serum levels of oxidative stress biomarkers in depressed patients in the acute phase as compared to those of healthy controls (Black *et al*., 2015). Present study reveals that banana pulp and peel extract both reduce the anxiety/fear like effects produced following exposure to elevated plus maze (Figure 1) and light dark activity test (Figure 2). It has been shown that emotional stress induces oxidative damage and considerably changes the balance between pro-oxidant and antioxidant factors in the brain (Fontella *et al*., 2005). Table 1 show that banana pulp and peel via their antioxidant potential increase activities of CAT, GSH and SOD in the brain. It is suggested that phyto-antioxidanst which are present in banana pulp and peel have strength to reduced anxiety/fear-like condition and regulated HPA-axis which play major role in fear situation.

FST developed, induces unavoidable stress to rodents which reflects a state of behavioral despair that is similar to human depression (Sakakibara *et al*., 2008). A normal animal tested in FST submitted to a non-soluble aversive situation shows alternate between agitation and immobility. The agitation reflects state of searching which requires energy consumption while immobility is energy conservation (Badhe *et al*., 2010). The uses of animal model are widely used as preclinical screening for antidepressant (Haider *et al*., 2016). Animals that are treated with antidepressants struggle more even in desperate situation and spend less time with immobility (Badhe *et al*., 2010). In the present study we have employed FST with the administration of banana pulp and peel extract to measure the antidepressant-like effects. A recent study showed that stem extract of *M. sapentium* also produced antidepressant like effect (Reddy *et al*., 2016). Antidepressant drug such as imipramine (Hellión-Ibarrola *et al*., 2016) and fluoxetine (Reddy *et al*., 2016) are also involved in reducing immobility time. There is a patho-physiological relationship between oxidative stress and depression. A meta-analysis conducted from 1990 to 2015, with 115 studies, comparing the oxidative stress markers between depressed patients and healthy controls found lower total antioxidant levels and higher oxidative damage in depressed patients than controls. It was further seen that there was an increase in the antioxidant levels and decrease in the oxidative damage product levels after antidepressant medication (Liu *et al*., 2015).

Previously it has been reported that FST induce such behavioral and physiological effects as activation of the HPA axis and an increase in the plasma corticosterone level (Racca *et al*., 2005). Antidepressant drug also involved in lowering the blood corticosterone levels and normalized the HPA-axis (Samad *et al.,* 2006). It is validated that both banana pulp and peel extract are involved in antidepressant like effects by their antioxidant potential (Table 1) which is involved in normalization of HPA-axis.

Memory impairment is correlated with a decrease in brain and plasma antioxidants. Several authors suggested the possibility that the increase in oxidative stress may result in a relative decrease in antioxidant enzyme activities (Sigueira *et al*., 2005). Acetylcholine is considered as one of the important neurotransmitter implicated in memory function. One of the major markers for cholinergic function is the determination of acetylcholinestrase (AChE) activity (Papandreou *et al*., 2011). Previous research suggested a link between AChE activity and memory function but a definite uniform pattern for this relationship is not defined. Perez *et al*. (2010) reported memory impairment by decreased AChE activity

following neonatal iron exposure, whereas Das *et al*. (2000) investigated AChE activity in male rats subjected to acute and chronic immobilization stress. They observed a significant decrease in AChE activity following acute stress. A pronounced increase in transfer latency time was observed in passive avoidance test as compared to that of control and chronically stressed groups, indicating a better cognitive ability in these rats.

Recently, polyphenolic compounds have received considerable attention since they have been shown to protect neurons against a variety of experimental neurodegenerative conditions including cognitive deficit (Baydas *et al*. 2003). Moreover rat administered with banana showed increases in learning and memory ability (Jing *et al.* 2011). Kumar *et al*. (2012) also reported that phenolic phyto-chemicals in banana not only reduce the neurotoxicity as well as reduce the risk of Alzheimer's disease. Our data reveals that, banana pulp and peel extract increased the short term memory as well as long term memory (Figure 4), and also increased the activities of antioxidant enzyme in the brain (Table 1), which may be attributed to the increased AChE activity in animals. We hypothesize that phytochemical present in banana pulp and peel improves the neuronal plasticity (Pereira and Maraschin, 2015) which in turn affects the brain neurotransmitter levels. It is suggested that phyto-chemicals present in banana pulp and peel via their potential antioxidants improves the memory by increasing the AChE activity to regulate brain neurotransmitter levels.

CONCLUSION

The findings of this research report support the hypothesis that phyto-chemical present in banana pulp and peel have therapeutic effects against anxiety, depression and memory impairment possibly by their antioxidant mechanism. We suggest supplementation of banana pulp and peel as a remedy of these impairments in order to enable the individual to adequately deal with daily exposure to stress.

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