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ORAL ADMINISTRATION OF GMVT EXERTS ANXIOLYTIC EFFECTS ON BEHAVIORAL ANIMAL MODELS BY INCREASING DOPAMINE METABOLISM IN RATS

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ABSTRACT

Dopamine (DA) or 3, 4-**d**ihydr**o**xy**p**henethylamin**e** is neurotransmitter involve in neurodegenerative disorder effecting through dopaminergic neurons of substantia nigra. Different herbs and herbal drug have great attraction to treat anxiety .Ginseng plant is a traditional plant use in china over two thousand year ago. Its use to cure many pharmacological condition .Its effects on neurotransmitter metabolisms. Recent study designed to observe the effect of GMVT on dopamine and its metabolites DOPAC concentration in whole brain of rats and anxiolytic effect of herb GMVT were analyzed by using light –dark box, elevated plus maze and open field box animal models. Data of present work show that GMVT exerts anxiolytic effect by increasing dopamine concentration in whole brain of rats.

Key words: Ginseng *malva verticillata* tea *(GMVT),* Dopamine (DA) or 3, 4-dihydroxyphenethylamine .3, 4-Dihydroxyphenylacetic acid (DOPAC), Open field box (OFB). Light dark box (LDB), Elevated plus maze (EPM).

INTRODUCTION

Numbers studies provide beneficial effect of herb and herbal drug on human health. Use of herbal drugs and mixture increasing day by day because it's less expensive, easily available and have fewer side effects as compare to synthetic medicines (Farhat, 2015). DA synthesize from tyrosine amino acid act as neurotransmitter in both animals and humans. Involve in many cognitive behavior & locomotors activity also play important role in blood regulation and feeding behavior .Destruction of dopaminergic neuronal path way in substantia nigra linked with different neurological disorder for example attention-deficit hyperactivity disorder (ADHD), addiction and Parkinson's disease (PD) (Wise, 2004; Hornykiewicz, 2006; Solanto, 2002). PD is progressive neurodegenerative diseases characterized by low dopamine function of neuron in the substantia nigra .Ginsenosides is a major constituent of ginseng plant use as neuroprotective agent (Wei, 2015).

Light dark box and EPM are well establishing animals models used to measuring anxiety in experimental animals. Activity in open filed box also use to measure the anxiety in laboratory animals .The aim of present study the effects of GMVT on the concentration of DA and their metabolites in rats brain and behavioral effects of animals in EPM, LDB and OFB animals models apparatus. Finding of behavioral apparatus and dopamine level help to study the anxiolytic effects of GMVT.

MATERIALS AND METHODS

Animals

24 Albino Wistar male rats weight between 280-320 grams were used. All animals were placed in separate cages under 12 h light-dark cycle and control room temperature (23±2^{o}C) with free access to specially prepared diet and water for one week, prior to starting the experiment so that rats could adopt themselves to new conditions.

Preparation of Extract

Fresh tea was prepared by boiling one tea beg in 100 ml of water for five minutes.

Experimental Protocol

The animals were divided into two experimental groups. The test group received 2ml GMVT. The control group received water, amount equivalent to that of aqueous G|M. Behavioral activities were monitored weekly in light dark box, elevated plus maz and open field box apparatus. After significant difference of behavioral activity rats were decapitated using guillotine. Brain samples were collected and stored at -70°C for the estimation of brain DA

and DOPAC. Estimation of monoamines (neurotransmitters) and their metabolites in the whole brain samples of rats was made by HPLC-EC method as reported by (Haleem *et al.*, 2004).

Statistical Analysis

The significance differences between the mean of the treated and untreated groups were analyzed by student's t-test. Values of $p < 0.05$ were considered as significant. Data expressed in figures as mean ±standard deviation (SD).

RESULTS

Effect of oral administration of GMVT on weekly elevated plus maze activity in rats:

GMVT show significant increase ($p<0.01$) in time spent in open arm while non significant effect on number of entries in closed arm from second week (Fig.1) as compared to control.

Effect of oral administration of GMVT on weekly light dark activity box in rats:

Three weeks oral administration of GMVT on light dark activity box. Significant increase ($p<0.05$) in time spent in light box (Fig. 2) were observed from week two while no significant effect on number of entries in dark box as compared to control.

Effect of oral administration of GMVT on weekly open field box activity in rats:

Rats treated with GMVT show Significant increase ($p<0.01$) in locomotion activity and no significant difference in corner sitting from first week (Fig.3) as compared to control.

Effect of oral administration of GMVT on whole brain DA and DOPAC levels in rats:

GMVT treated rats shows significant increase in brain DA ($p<0.01$) (Fig.5) and DOPAC ($p<0.05$) (Fig.6) levels in rats as compared to control.

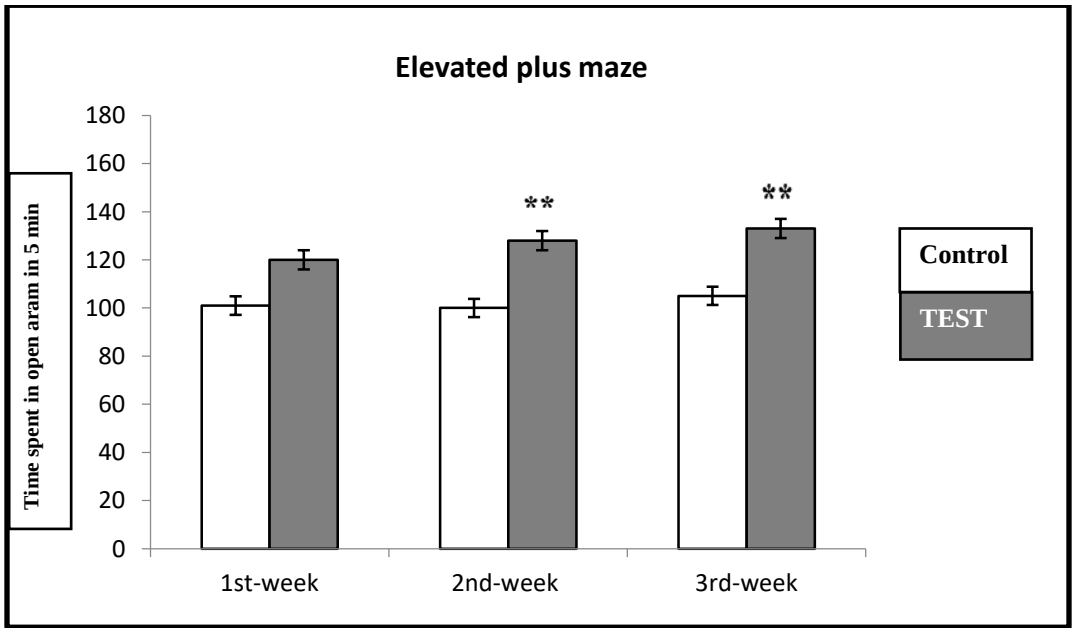

Fig. 1. Effect of repeated administration of GMVT on elevated plus maze activity (time spent in open arm) of rats. Values are mean ± SD (n=12) significant difference by Student *t*-test **p<0.01 from respective controls.

DISCUSSION

Behavior of treated rats in EMP show significant increasing in time spent in open arm (Fig.1) from second week as compare to control animals. Animals treated with GMVT like to stay in open arm .EMP have two open and two closed arm .Anxiolytic effects indicates in the EPM by increasing the ratio of time spent in open arm (Pellow,1985; Treit, 1993; Rodgers, 1997; Carobrez, 2005). LDB also use in this study to elevate the anxiolytic effects of GMVT. It consists of one dark and on light (transparent) box .It is very useful apparatus to study anxiogenic and anxiolytic

effects of drugs. Statistical analysis show significant (Fig. 2) increase in time spent in light box from second week while no significance effect were observe in number of entries in dark box. GMVT produce anxiolytic effect in animals and due to these effect rats spent more time in light box and did not go in the dark box while rates treated with anxiogenic drug produce fear in rats which in turn increase the spending time of rats in dark box (Borsini, 2002). OFB is use full tool used to monitor general locomotors activity level and anxiety in animals (Kathleen, 2014; Denenberg, 1969; Blizard, 2007).

Present research show significant increase from first week (Fig. 3) in locomotors activity and significant decrease in corner sitting (Fig. 4) time. Anxiolytic drug increase locomotors activity & decrease corner sitting time of animal in open field box. Anxiolytic drug increased exploratory activity & decrease sitting time in corner of box (Stanford, 2007).

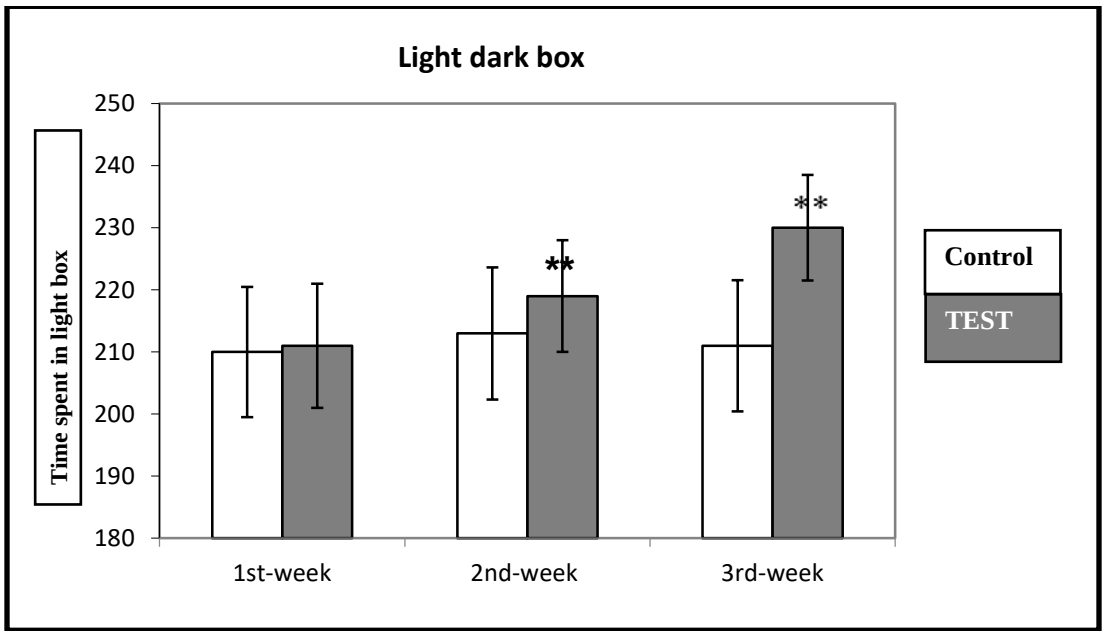

Fig. 2. Effect of GMVT on light dark activity (time spent in light box) of rats. Values are mean ± SD (n=12) significant difference by Student *t*-test **p<0.01 from respective controls.

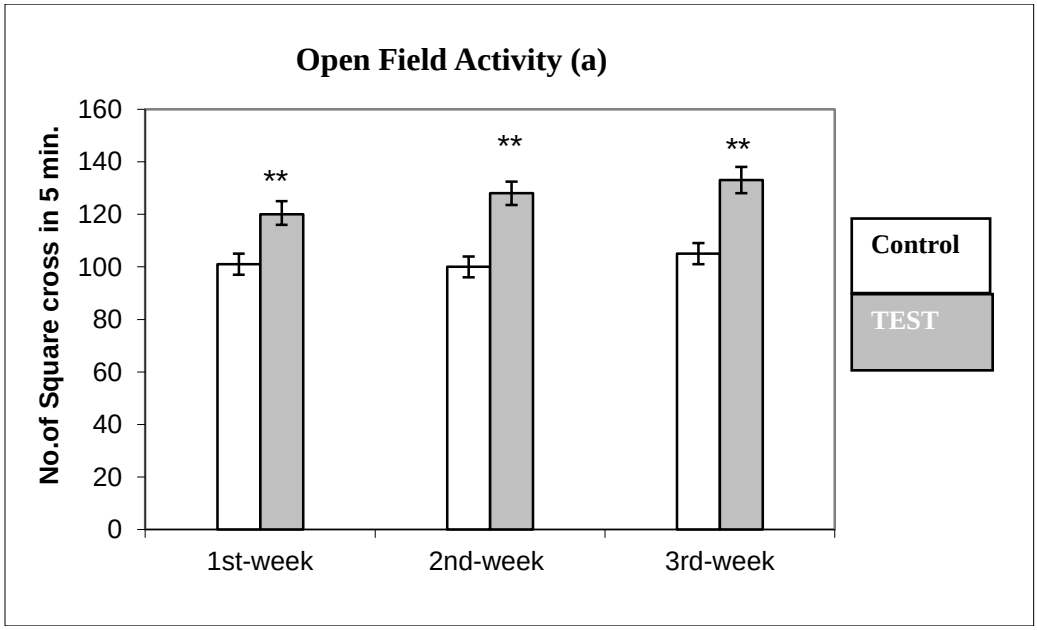

Fig. 3. Effect of repeated administration of GMVT on open field activity (square cross)of rats. Values are mean ± SD (n=12) significant difference by Student *t*-test **p < 0.01 from respective controls.

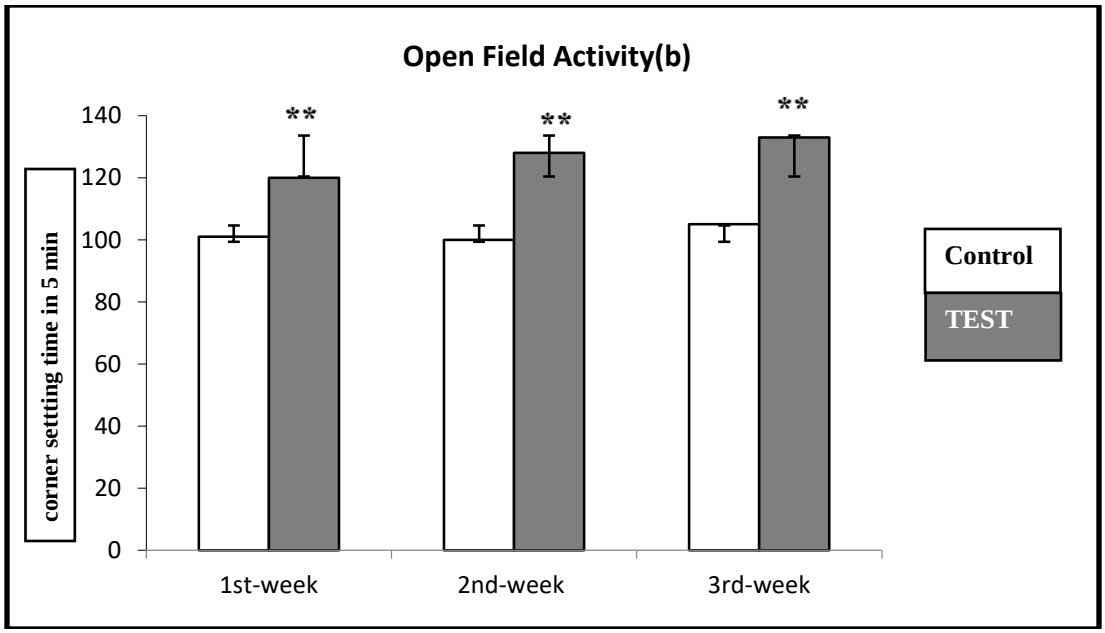

Fig. 4. Effect of repeated administration of GMVT on open field activity(time setting in corner) of rats. Values are mean ± SD (n=12) significant difference by Student *t*-test **p<0.01 from respective controls.

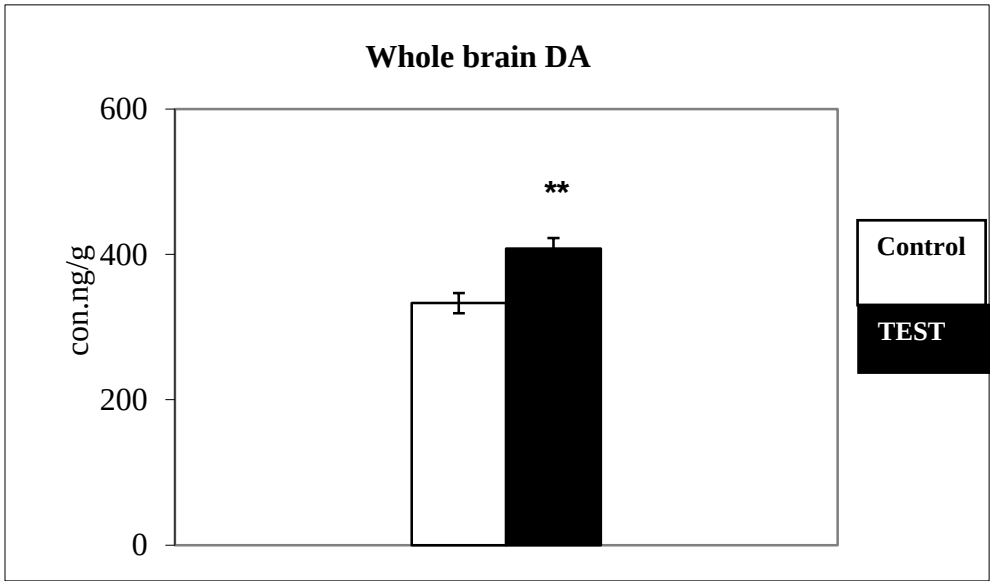

Fig. 5. Effect of repeated administration of GMVT on DA level of rat's brain. Values are mean ± SD (n=12) significant difference by Student *t*-test **p < 0.01 from respective controls.

Many researchers reported that ginsenosides involve in release of neurotransmitter in the brain (Xue, 2006; Liu, 2014). Data of present research show significant increase in dopamine level (figure.5) and significant decrease in DOPAC level (Fig. 6) in whole rat's brain as compare to control rats. Anxiolytic effect of GMVT might be due to high concentration of dopamine in brain. Its agreement with (Xiang *et al*., 2011) who reported saponins constituent of ginseng produce antidepressant effect by increasing dopamine and noradrenalin in brain. It is well establish that dopaminergic system is a key element in the control of locomotion (Juan *et al.*, 2010). Deficits of DA are associated with Parkinson's disease20. It is clear that PD is effect in the locomotors controlling region in brain. Ginseng plant and their isolated component have been reported for their antidepressant(Chen *et al*., 2014; Cui *et al*., 2012; Dang *et al.*, 2009; Xu *et al.*, 2010) anxiolytic (Jeong *et al.*, 2005) anti-parkinsons (Van *et al.*,2014; González *et al.*, 2015)and anti-alzihemier (Fang *et al.*, 2012; Heo *et al.*, 2011) properties. Neuroprotective produce through inhibition of oxidative stress and inflammation and other several activities in brain (González *et al.*, 2014). GMVT

oral administration increased locomotors activity in treated rates .its agreement with previous researcher that reported active parts of ginseng plant reduce locomotors dysfunction in laboratory designed PD experimental animals (González, 2015; Wei *et al.,* 2015; Suk, *et al.,* 2011). Present research result and previous research strongly support that GMVT can be use to improve Parkinson like symptoms and also provide neuroprotective effects.

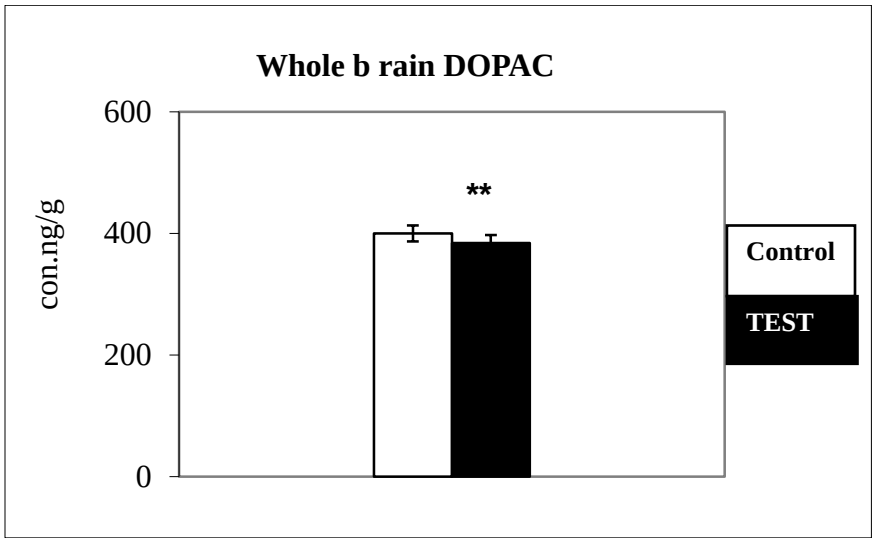

Fig. 6. Effect of repeated administration of GMVT on DOPAC level of rat's brain. Values are mean ± SD (n=12) significant difference by Student *t*-test **

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