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# Anxiolytic, antidepressant and inhibitory effect on MAO isoenzymes by *Bougainvillea glabra* flower extract in rats

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**Abstract**: Main aim of current study was to determine the anxiolytic and antidepressant potential of *Bougainvillea glabra* Extract (BVE). The effects were investigated by using Open-Field-Test (OFT), Light-and-Dark Model (LD), Hole-Board (HB) and Forced-Swimming-Test (FST). Different doses for BVE were given to Wistar-Rats and compared with Control and Diazepam. Data has been collected by simple observations of animal behaviors in mentioned models. Collected data was analyzed by SPSS-22 version. In OFT (number of squares travelled), significant differences noted between Control and BV100mg/kg (p=0.001), Diazepam and BV100mg/kg (p=0.0001), Diazepam and BV200mg/kg (p=0.015), Diazepam and BV300 mg/kg (p=0.002). In LD-Test, significant differences were noted between Control and BV100mg/kg, BV200mg/kg and BV300mg/kg (p=0.0001), Diazepam and BV100mg/kg, 200mg/kg (p=0.0001), Diazepam and BV300mg/kg (p=0.028). In HB-Test by head dips, significant differences noted between control group and BV100mg/kg and 200mg/kg (p=0.0001), Control group and BV300mg/kg (p=0.005). For number of head dips, significant differences noted between Diazepam and BV100mg/kg, 200mg/kg and 300mg/kg (p=0.0001). In FST, significant differences were observed between Control group and BV100mg/kg, BV200mg/kg and BV300mg/kg (p=0.0001), Fluoxetine and BV100mg/kg, BV200mg/kg and BV300mg/kg (p=0.0001). It is observed that MAO-A and MAO-B are inhibited by BVE. Study demonstrates that BV flowers have anxiolytic and antidepressant activities.

**Keywords**: *Bougainvillea,* flower extract, anxiolytic, antidepressant, monoamine oxidase – A, monoamine oxidase - B

## INTRODUCTION

With the passage of time neurological problems among the civilized human have risen dramatically. Nowadays the global pandemic of Covid-19 infection has led to stress and anxiety among the many economic classes of population (Mann *et al.*, 2020). This has long lasting effects among the population of developing countries with limited health and financial resources (Jung *et al.*, 2019). Many surveys in various countries revealed that the number of patients of depressive disorder among all age groups including healthcare practitioners, household women, college and university students have increased (Knowles and Olatunji, 2021). According to one study, 25.4% patients reported deterioration of their mental health since the beginning of COVID-19 pandemic, among them 19% developed depression and 14% developed generalized anxiety disorder (Choi *et al.*, 2020).

Nature has bestowed the universe with countless blessings including the plant kingdom for the management of different diseases (Kim *et al.*, 2020). These plants not only provide food but play a vital role in maintaining health of living being (Da-Yong and Ting-Ren, 2019). To promote the neuropsychological well-being among all the segments of population, we must find the remedy from natural treasures available locally in Pakistan. In clinical practice there are numerous prescription drugs are available to treat depression and anxiety but these treatments have many adverse effects, the most severe is suicide attempts (Read and Williams, 2018). However, many natural remedies and herbal medicines reduce the adverse effects of conventional treatments when used in combination (Sarris, 2018).

By keeping these options for the treatment of anxiety and depression, primary end-point of study was to explore the neurologic potential of the compounds existing in BV (*Bougainville*) at different doses. Some species of *Bougainvillea glabra* are already established as an alternative medicine in the management of human diseases (Abarca Vargas and Petricevich, 2018). Hundreds of research articles published on BV leave extracts (AbarcaVargas *et al.*, 2016, Narayanan *et al.*, 1987, Narayanan *et al.*, 1984) but limited work has been performed on flower extracts regarding neuro-pharmacological activities. Monoamine oxidase (MAO) is a key enzyme that is associated with the metabolism of neurotransmitters associated to psychopathology. Its activity has been suggested as a key indicator of disease progression (Pan *et al.*, 2005). Due to this reason another end-point of study was to determine the effect of BVE on MAO enzymes.

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## MATERIALS AND METHODS

### *Study Design*

Prospective experimental study was conducted in Pharmacology Research Laboratory of Faculty of Pharmacy, Hamdard University, Karachi. Workout has been performed on in-vivo and in-vitro parameters. The duration of study was from June 2020 to June 2021.

### *Plant Material*

Fresh BV (*Bougainvillea*) flowers were collected from the University of Karachi and authenticated by a botanist in the Botany Department, University of Karachi, Pakistan. The voucher specimen (G. H. No. 94814) was issued. Flowers (1Kg) were washed thoroughly and cut into small pieces followed by soaking in 2 Liters 70% of water: ethanol solvent mixture for three days. The resultant mixtures were filtered. The filtrate was dried at 40°C using rotary evaporator. The percentage yield of the extract was approximately 4.9% w/w dry matter.

### *Animals*

The study included 36 Wistar rats obtained from the Animal House of ICCBS (International Center for Chemical and Biological Sciences), University of Karachi. Male rats of weight 150-200 grams were selected, acclimatized for 7 days in cages, provided food and water at 25±1°C with a 12-hour light-dark cycle. The animals were assigned to six different groups and each group having comprised of six animals.

Group 1 - Control (CT) - received distilled water (10 ml/kg, P.O)
Group 2 - Diazepam 1 mg/kg (I.P)
Group 3 - Fluoxetine 20 mg/kg (I.P)
Group 4 - BVE (*Bougainville* Extract) 100mg/kg (P.O)
Group 5 - BVE (*Bougainville* Extract) 200mg/kg (P.O)
Group 6 - BVE (*Bougainville* Extract) 300mg/kg (P.O)

### *Chemicals and Drugs*

Diazepam, Fluoxetine, hydroalcoholic extracts were used and stored at 8°C. Drugs and extracts brought to room temperature before performing pharmacological activities on animals.

### *Acute Toxicity Evaluation*

Acute toxicity study was carried out according to the Organization of Economic Corporation Development (OECD) guidelines No. 425 (OECD, 2008). BVE were administered orally in doses of 100, 200, 400, 800, 1000 and 2000 mg/kg to Rats ($n$=3) and the percentage mortality was recorded for a period of 24-hour. During the first 1-hour after the drug administration, the gross behavioral changes like hyperactivity, grooming, convulsions, sedation, loss of righting reflex, respiration, salivation, urination and defecation were observed carefully.

### *Open Field Test (OFT)*

Open Field paradigm (Zimcikova *et al.*, 2017) consisted of a plain floor surrounded by transparent acrylic walls 30cm high. The floor is divided in 25 equal squares having dimension 15x15cm$^2$. The animal were placed individually in the corner of the field and allowed to move freely. For the time period of 5 minutes following parameters were noted; number of central squares travelled and time spent in central squares. Counting of square considered when rat enter in square with all four paws.

### *Light and Dark Test (LD)*

The apparatus (Abid *et al.*, 2017) used was a two compartment box with equal size (26x27x28cm) and a midway door of 10x10cm. One half was made dark by totally covering it, whereas a 40-W lamp illuminated the other half. The light source was placed 35cm above the transparent box. The rats were treated with BV (100, 200 and 300mg/kg, P.O), Diazepam (1mg/kg, I.P.) or vehicle 30 minutes before being placed individually in the center of the light box and time spent in light box was recorded by movie recorder for the next 5 minutes. Later on time was further verified by stop watch. Percentage time was calculated by (time spent in light box / Total time spent in LD)*100.

### *Hole Board Test (HB)*

Composition of the Hole Board is acrylic chamber (Dimensions; 40x40x25cm$^3$), floor of the hole board having 16 equal sized holes i.e. 3cm in diameter and distributed evenly (Casarrubea *et al.*, 2015). For the rats to peep through the holes, the floor of apparatus was elevated at height of 25 cm from the ground. 30 minutes before test animals were administered with distilled water P.O, Diazepam I.P and BVE 100mg/kg, 200mg/kg and 300mg/kg P.O. The individual animal was kept into the hole board apparatus and allowed to move freely. For the next five minutes total number of head dips and the duration of head dips were recorded.

### *Forced Swimming Test (FST)*

This test (Abbasi-Maleki *et al.*, 2020) is used for analyzing depression like behavior in rodents. In this test a tank was used with dimensions of 56cm (height), 20cm (width). The temperature of tank was kept at 25ºC±1 and height of water at 22 cm. Rats were forced to swim for six minutes in this tank. In initial stage, the animal struggled to escape but eventually it exhibited immobility. The level of water was kept high enough to prevent the animal body to touch the bottom of tank while preventing escape from tank. The immobility time was calculated for the last five minutes. Immobility means, no further attempt to escape except the minimum movement to keep nose above the water level.

### *MAO-A Inhibitory Activity*

Brain was obtained by cervical dislocation and stored at -80°C. 0.3M sucrose was used for suspension of brain to get monoamine and 15 minutes centrifugation was done initially at 2500 rpm, supernatant was collected. Collected

supernatant was again suspended in sucrose and then centrifuged to re-extract enzyme. After this process, supernatant was centrifuged at 17000xg for 15 minutes at 4°C, the extracted enzymes were stored in the form of pellets. Phosphorus buffer was used to suspend these pellets with inhibitor for any specific analysis. Enzyme inhibitory activity was measured by 96 well-plate ELISA reader in 20 micro-litre diluted solution. The material used were MAO-A (Monoamine Oxidase) Kit (Biovision; Catalog No. K796-100), USA, amplex red reagent, $H_2O_2$, DMSO, MAO-A substrate p-tyramine, 5x reaction buffer, horseradish peroxide and MAO-A inhibitor clorgylin. Fluorescence was measured at Ex/Em = 535/587nm using Spectrofluorimetric method (Badavath *et al.*, 2016). Animal isolated enzyme, equimolar strength substrate, test compound and mixture of buffers was contained in every well of 96 well-plate. After incubation of 15 minutes at 37°C, inhibition was measured by black well-plate. $H_2O_2$ produced when general enzyme and MAO reacted. Amplex red reagent react with $H_2O_2$ in the presence of horseradish peroxide, this reaction results in the production of illuminating resorufin. The concentration of resorufin indicates the presence or absence of MAO-A.

***MAO-B Inhibitory Activity***

Whole method is same as mentioned above for MAO-A, except for some variation like added pargyline instead of clorgyline and change the inhibitor from p-tyramine to benzylamine.

## STATISTICAL ANALYSIS

Primary data was collected by animal observations for anxiolytic and antidepressant activity of BV. The data was analyzed by One-Way ANOVA test with LSD (Least Significant Difference) and descriptive statistics through SPSS-22 Version software. Confidence Interval was 95% and level of significance was at $p<0.05$.

## RESULTS

In acute toxicity study as per OECD guidelines (OECD, 2008) no mortality and abnormal behavior pattern observed in any subject animals.

In OFT the no of central squares travelled have significant differences among all groups (ANOVA, F=10.33, p=0.0001). Similarly, for number of squares travelled, significance is noted between Control (CT) and BV 100mg/kg (p=0.001), Diazepam and BV 100mg/kg (p=0.0001), Diazepam and BV 200mg/kg (p=0.015), Diazepam and BV 300mg/kg (p=0.002), BV 100mg/kg and BV 200mg/kg (p=0.007), BV 100mg/kg and BV 300mg/kg (p=0.049). fig. 1a

Anxiolytic activity was noted by Open Field Test (OFT) methods in Control (CT) group, Diazepam group and BV 100mg/kg, BV 200mg/kg and BV 300mg/kg groups. Time spent in central squares have significant differences among all groups (ANOVA, F=8.48, p=0.0001). As far as time spent in central squares, according to LSD, significant difference observed between control group and Diazepam group (p=0.001), control and BV 100mg/kg (p=0.031), Control and BV 300mg/kg (p=0.048), Diazepam and BV100 mg/kg, BV 200mg/kg, BV 300mg/kg (p=0.0001), BV 200g/kg and BV 300mg/kg (p=0.017). fig. 1b

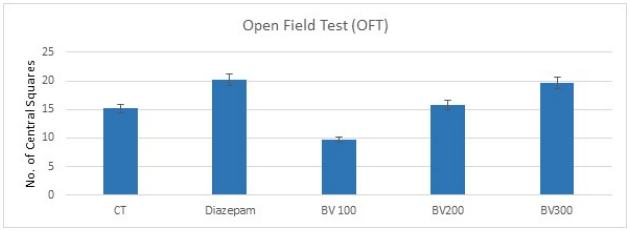


**Fig 1a**: No of Central Squares travelled in OFT (F-test, Significance at $p<0.05$)

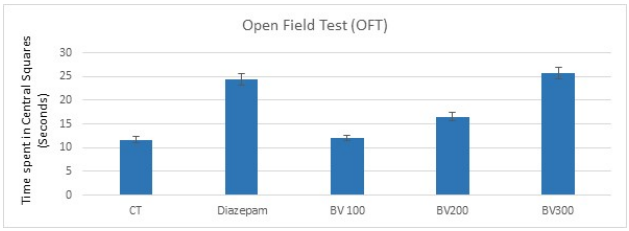


**Fig 1b**: Time spent in Central Squares in OFT (Significance at $p<0.05$)

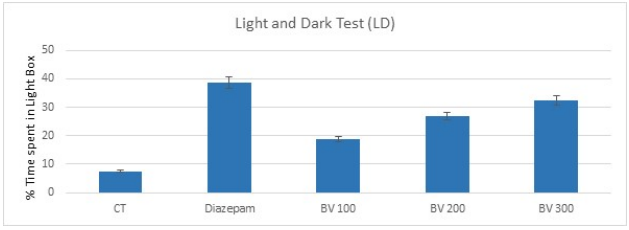


**Fig 2**: Time spent in Light Box in LD (Significance at $p<0.05$)

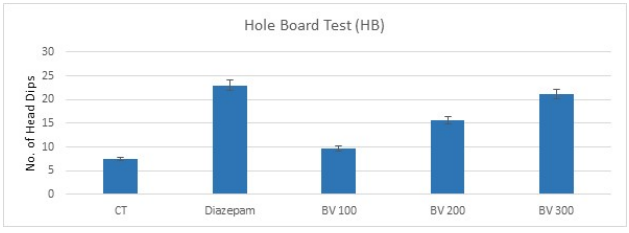


**Fig 3a**: Number of Head Dips in HB (Significance at $p<0.05$)

Anxiolytic activity was noted by Light and Dark Test methods in Control (CT) group, Diazepam group and BV 100mg/kg, BV 200mg/kg and BV 300mg/kg. Overall significant difference is noted among groups (ANOVA, F=40.97, p=0.0001). In multiple comparison by LSD, significant differences are noted in between Control group

and Diazepam, BV 100mg/kg, BV 200mg/kg and BV 300mg/kg (p=0.0001), Diazepam and BV 100mg/kg, BV 200 mg/kg (p=0.0001), Diazepam and BV 300mg/kg (p=0.028), BV 100mg/kg and BV 200mg/kg (p=0.006), BV 100mg/kg and BV 300mg/kg (p=0.0001) fig. 2

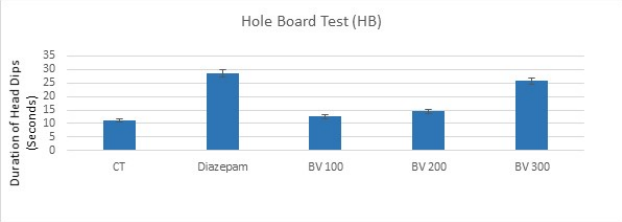


**Fig 3b**: Duration of Head Dips in HB (Significance at p<0.05)

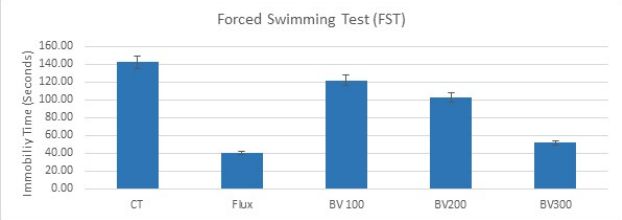


**Fig. 4**: Immobility Time in FST (Significance at p<0.05)

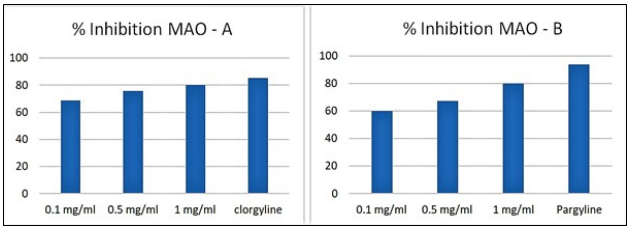


**Fig. 5**: MAO - A and MAO - B % inhibition by BVE in comparison with substrate

Anxiolytic activity was noted by Hole Board Test methods in Control (CT) group, Diazepam group and BV 100mg/kg, BV 200mg/kg and BV 300mg/kg. Number of head dips (ANOVA, F=22.31, p=0.0001) are significantly different among groups. As far as concerned with head dips, Significant differences are noted in between Control group and Diazepam (p=0.001), Control group and BV 100mg/kg and BV 200mg/kg (p=0.0001), Control group and BV 300mg/kg (p=0.005). Similarly for number of head dips, significance is noted in between Diazepam and BV 100mg/kg, BV 200mg/kg and BV 300mg/kg (p=0.0001), BV 100mg/kg and BV 200mg/kg (p=0.016), BV 200mg/kg and BV 300 mg/kg (p=0.0001). Significant differences in duration of head dips are in between Control group and BV 100mg/kg, 200mg/kg and 300mg/kg (p=0.0001), Diazepam and BV 100mg/kg, BV 200mg/kg and BV 300mg/kg (p=0.0001), BV 200mg/kg and BV 300mg/kg (p=0.034) fig. 3a

Duration of head dips (ANOVA, F=20.44, p=0.0001) are significantly different among groups. Significant differences in duration of head dips are in between Control (CT) group and BV 100mg/kg, BV 200mg/kg and BV 300mg/kg (p=0.0001), Diazepam and BV 100mg/kg, BV 200mg/kg and BV 300mg/kg (p=0.0001), BV 200mg/kg and BV 300mg/kg (p=0.034) fig. 3b

Antidepressant activity was noted by Forced Swimming Test (OFT) methods in Control (CT) group, Diazepam group and BV 100mg/kg, BV 200mg/kg and BV 300mg/kg. Overall significant difference is noted for percent immobility time among groups (ANOVA, F=171.89, p=0.0001). In multiple comparison of groups by LSD, significance is noted in between Control group and Fluoxetine, BV 100mg/kg, BV 200mg/kg and BV 300mg/kg (p=0.0001), Fluoxetine and BV 100mg/kg, BV 200mg/kg and BV 300mg/kg (p=0.0001), BV 100mg/kg and BV 200mg/kg (p=0.002), BV 100mg/kg and BV 300 mg/kg (p=0.0001), BV 200mg/kg and BV 300mg/kg (p=0.0001) fig. 4

In vitro assay of MAO - A and MAO - B run at different concentrations of BVE 0.1mg/ml, 0.5mg/ml and 1mg/ml with standard substrate. BVE has shown dose dependent inhibition of MAO - A (68.7% at 0.1mg/ml, 75.8% at 0.5 mg/ml, 80% at 1mg/ml) and MAO - B (60.13% at 0.1 mg/ml, 67.17% at 0.5mg/ml, 79.87% at 1mg/ml) with respect to substrate for MAO - A (clorgyline) and MAO - B (pargyline) fig. 5

## DISCUSSION

Crude extract of BV plant has demonstrated several activities in human body e.g. antibacterial, antifungal, antidiabetic, cytotoxic, analgesic, antipyretic, anti-inflammatory and antioxidant (Saleem *et al.*, 2020, Narayanan *et al.*, 1987). The present experimental study demonstrates for the very first time the potential anxiolytic and antidepressant activities of native Pakistani BV flower. Current study also examined the anxiolytic activity by Open Field test (Zimcikova *et al.*, 2017), mean number of central squares for BV 300mg/kg (19.67±2.06) and Diazepam (20.16±2.05) are almost similar. Shastry *et al* also have similar findings about *Camellia sinensis* in Rats, where increase in number of central squares crossed confirmed anxiolytic activity (Shastry *et al.*, 2016). Similar findings were also noted in mean duration of central squares travelled i.e. BV 300 mg/kg (25.66±2.29 Sec.) and Diazepam (24.33±1.25 Sec.). *Apium graveolens* also increase the time spent in the central arena, which supports current study findings about anxiolytic activity (Tanasawet *et al.*, 2017). In time spent in central square measurement, it is noted that BV 300mg/kg and 200mg/kg are significantly better in anxiolytic activity compared to control group, however, apparently there is no difference in between Control group and BV 100mg/kg. As far as concerned with Diazepam, BV100mg/kg, BV 200mg/kg and BV 300mg/kg are having significantly lower anxiolytic activity compared

with Diazepam. Although no difference is apparent in between Diazepam and BV 300mg/kg. Interestingly in the number of central squares travelled, significant difference was noted in between Control and BV 100mg/kg (p=0.0001). However, BV all strengths are significantly lower in anxiolytic activity compared with Diazepam, which is also reflected in other standard tests.

Anxiolytic activity of BV 100mg/kg, BV 200mg/kg and BV 300mg/kg was compared with control and standard drugs by Light and Dark test in rats.(Abid *et al.*, 2017) Mean time spent in light box was lowest for control group (7.55±0.96 Seconds), while higher time were noted for BV 300mg/kg (32.44±1.42 Seconds) and Diazepam (38.77±2.06 Seconds). In current model, BV all three doses were having significantly better anxiolytic activity compared with control drug (p=0.0001), however, the anxiolytic activity of all three doses of BVE were significantly lower than Diazepam, nevertheless, apparently BV 300mg/kg was showing similar anxiolytic activity compared to Diazepam. In addition, it is noted that among all three doses, BV 300mg/kg was significantly better in terms of anxiolytic activity (p=0.0001). Increase time spent in illuminated box also confirmed the anxiolytic activity of *Persicaria hydropiper* in one of the study (Shahed-Al-Mahmud and Lina, 2017).

Hole Board test method is also one of the standard test to determine the anxiolytic activity of substances (Casarrubea *et al.*, 2015). In this test mean number of head dips were lowest for control group (7.5±0.99), while higher values were reported for BV 300mg/kg (21.16±1.85) and Diazepam (23±0.96). For the mean duration of head dips, again control group had lowest value (11.16±1.30 Seconds), while higher values were reported for BV 300mg/kg (25.66±2.07 Seconds) and Diazepam (28.5±1.72 Seconds). By examining the anxiolytic activity through head dips, BV all strengths have significantly (p=0.0001) better anxiolytic activities compared to Control group, while all these dose of BV were not better than Diazepam. In the similar way, BV 200mg/kg was significantly better than BV 100mg/kg (p=0.0001) and BV 300mg/kg was better than BV 200mg/kg (p=0.0001). As far as concerned with duration of head dips, again BV all strengths have shown significantly (p=0.0001) better anxiolytic activity compared to Control group, while Diazepam was better than all three strengths of BV extracts. In addition to this BV 300mg/kg was significantly better in terms of anxiolytic activity compared to BV 200mg/kg. Positive impact in head dip/poking is an strong indicator of anxiolytic potential of any substance as same is shown in current study (Begum and Younus, 2018).

Behavioral despair model such as Forced Swimming test is the fast and efficient way for the determination of antidepressant activity in rodents (Abbasi-Maleki *et al.*, 2020). Clinical drugs such as Tricyclic Antidepressants (TCA) and Selective Serotonin Receptor Inhibitors (SSRI) increase the animal activity and significantly reduce immobility time that is the core indictor of the antidepressant activity (Sanmukhani *et al.*, 2011). In this test, mean immobility was highest in control group (142.50±4.46 Sec.) and lowest in Fluoxetine group (36.17±2.32 Sec.), which is relatively comparable with BV 300mg/kg (55.17±2.46 Sec.). BV 100mg/kg, 200mg/kg and 300mg/kg, all these strengths have shown significantly lower immobility time compared to control group (p=0.0001), which proves that all doses have antidepressant activity in-contrast to control group. Nevertheless, Fluoxetine have shown significantly better antidepressant activity against all three strengths of BVE. Apparently, BV 300mg/kg and Fluoxetine have similar antidepressant activity.

Strongest evidence, which has been generated from current study regarding antidepressant activity, is inhibition of Monoamine Oxidase enzymes by BVE. MAO – A enzyme is available predominantly in brain, its excess may lead to CNS depression (Du *et al.*, 2002). As BVE inhibited the MAO – A enzyme, i.e. why its inhibition is increasing bioamines in brain and leading to antidepressant activity same like Tranylcypromine (Reed *et al.*, 2008). Compounds having suspected neuro-pharmacological activities in BV flower hydroalcoholic extract are tannins, flavonoids, alkaloids and phenolic compounds (Sahu and Saxena, 2012).

## CONCLUSION

The present experimental study demonstrated the anxiolytic and strong antidepressant activities in the flowers extract of native Pakistani *Bougainvillea glabra*. The compounds in BVE showed dose dependent MAO-A and MAO-B inhibitory activity. These in-vivo and in-vitro results clearly demonstrated the anxiolytic and antidepressant effects of BVE in CNS models.

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