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DRUG DISCOVERY

Evaluation of Antidepressant activity of *Bacopa monnieri* in rat: A study in Animal Model of Depression

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ABSTRACT

Major depression is a common and potentially life threatening condition. Stress induced helplessness in rodents constitutes a well-defined model to investigate physiological attributes of depression. The present study was undertaken to determine the antidepressant property of *Bacopa monnieri* using the stress induced animal model of depression. In this study, we have confirmed the actual doses of administration of this herbal product for recovery from stress related disorders in rats. Acute treatment with *Bacopa monnieri* extract *of* 80 and 120 mg/kg body weight, significantly reduced escape latency and plasma corticosterone level along with the significant restoration of body weight among the stressed rats. Such properties of Bacopa extract clearly coincides with the effects of well accepted antidepressant drug Fluoxetine hydrochloride and prominently fore cast the antidepressant property of *Bacopa monnieri* in stress related neuropsychiatric disorders.

Key words: Antidepressant, Bacopa, Depression, Fluoxetine, LH, Corticosterone.

Abbreviations: BM- *Bacopa monnieri*, LH- Learned Helplessness, FLX- Fluoxetine hydrochloride.

Animal model of Depression: Animal models of depression are research tools used to investigate depression and action of antidepressants as a simulation to investigate the symptomatology and pathophysiology of depressive illness or used to screen novel antidepressants.

1. INTRODUCTION

Psychiatric disorder is a life threatening illness that affects millions of people worldwide. According to World Health Organization, depression is now the fourth most prevalent cause of loss of manpower and it will become the second by the year 2020. Depression can lead to suicide, a tragic fatality associated with the loss of 10.50 lives per 100,000 people in every year in India. Recent studies reported that depression and anxiety may occur together in association with sub threshold level of depression and anxiety. Anxiety may also predispose depression or vice-versa or symptoms of anxiety and depression may be external manifestation of underlying cause. A triad of clinical symptoms characterizes depression: low or depressed mood, anhedonia, and low energy or fatigue. Other symptoms, such as sleep and psychomotor disturbances, suicidal tendencies, decreased food-intake and body-weight are also often present (Banerjee et al., 2011a and Banerjee et al., 2011b).

Commonly antidepressant drugs available for the treatment of neuropsychiatric disorders are MAOI, SSRIs, SNRIs and NRIs but these drugs only produce remission in 30% of patients because multiple pathogenic factors are involved in depression and also there are severe side effects while treated with those drugs. So, drugs having properties to combat both anxiety and

Somoday Hazra et al.
Evaluation of Antidepressant activity of *Bacopa monnieri* in rat: A study in Animal Model of Depression,
Drug discovery, 2012, 2(4), 8-13,

CHEMICAL COMPOSITION OF BM

The herb contains the alkaloids brahmine, herpestine, and a mixture of three bases. It also contains the saponins, monnieri; hersaponin, bacoside A and bacoside B. Other constituents present in the plant are D-mannitol, betulic acid, ß- sitosterol, stigmasterol and its esters, heptacosane, octacosane, nonacosane, triacontane, hentriacontane, dotriacontane, nicotine, 3-formyl-4-hydroxy-2H-pyran, luteolin and its 7-glucoside. The presence of a-alamine, aspartic acid, glutamic acid and serine is also reported.

Antidepressant: An antidepressant is a psychiatric medication used to alleviate mood disorders, such as major depression and dysthymia and anxiety disorders such as social anxiety disorder. According to Gelder, Mayou & Geddes (2005) people with a depressive illness will experience a therapeutic effect to their mood; however, this will not be experienced in healthy individuals. Drugs including the monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), tetracyclic antidepressants (TeCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) are most commonly associated with the term. These medications are among those most commonly prescribed by psychiatrists and other physicians, and their effectiveness and adverse effects are the subject of many studies and competing claims.

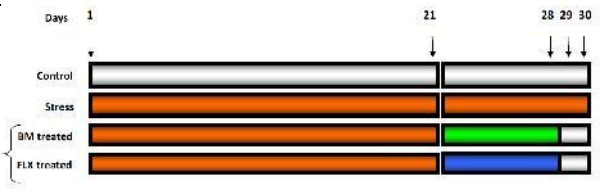

Figure 1

Schematic overview of the 30-day experimental protocol. Control Group: rats were subjected to no footshocks. Stress Group: rats received footshocks daily for 21 days followed by 9 days of alternating exposure to the footshocks. BM Treated Recovery Group: rats received footshocks daily for 21 days followed by a 7-day acute BM treatment instead of footshocks. FLX Treated Recovery Group: rats received footshocks daily for 21 days followed by a 7-day acute FLX administration instead of footshocks. The escape test was performed five times (day1, 21, 28, 29 and 30) during the entire 30 days stress paradigm.

depression with lesser side effects might be useful for such clinical conditions. Herbal products have recently become the drugs of choice and investigated for the search of novel and better tolerated molecules from plant sources (Zhang, 2004). Therefore, it is desirable to seek new antidepressants through herbal treatment. Herbal medicines are commonly used in healthcare programmes worldwide. Ancient pharmacopoeias from different regions of the world have recorded numerous herbal medicines purported to have psychotropic potential. These offer a vast repertory of potential substances that can be developed into modern psychiatric pharmaceuticals. The search for novel pharmacotherapy from medicinal plant for psychiatric illness has progressed significantly in the past decades for their therapeutic potential.

Bacopa monnieri (BM) is a perennial creeping annual plant found throughout the India in wet, damp and marshy areas (Satyavati et al., 1976). Commonly known as Brahmi, the plant has been used to increase intellect and memory for almost 3000 years by ayurvedic medical practitioners (Singh et al., 1982). Triterpenoid, saponins and bacosides present in BM (Rastogi et al., 1994) are considered to be responsible for enhancing cognitive function which helps to enhance memory (Udupa et al., 1995). Previous studies reported that it has potent neuropsycopharmacological activities in stress induced models in rats (Dhawan et al., 1996).

According to pharmacological profile of BM, it is reasonable to assume that the extract may have some neuro protective activities. Therefore, the present study was designed to investigate the anti-anxiolytic (Bhattachariya et al., 1998) and anti-depressant effects of BM extracts by using learned helplessness test (Sairam et al., 2002), the extensively validated and widely used stress induced model of depression in rats. Prior exposure to inescapable stress produces deficits in escape testing and evaluation was done by using shuttle box escape test. This animal model offers an opportunity to understand the behavioral correlation of clinical depression and efficacy of antidepressant drugs that have been investigated.

2. MATERIALS AND METHODS

2.1. Animals

Male Sprague-Dawley rats were used in the current experiment. At the start of the experiment, rats were of the same age (approximately 2 months) weighing 224±1.5 gm. All rats were individually housed in temperature controlled (22–24°C) room for at least 1 week prior to the experimentation, with *ad libitum* access to food and water. Rats were maintained on a 12 h light/dark cycle (lights on at 7 a.m.). All experimental protocols were designed to minimize the number of animals and sufferings were approved by the Institutional Animal Ethics Committee (IAEC) of the Raja Peary Mohan College, Uttarpara, West Bengal. Socially housed male rats were randomly assigned to 4 experimental groups prior to the experiment (Fig.1).

Control group (n = 10): subjected to no foot shock throughout the experiment.

Stress group (n = 10): received 60 foot shocks daily for first 21 days followed by next 9 days with alternating exposure to foot shocks.

Recovery group I, treated with *Bacopa monnieri* (BM) (n = 30): exposed to foot shocks daily for 21 days. Then the stressed rats were subdivided into three subgroups depending upon the graded doses of BM. Each group was administered once daily dose of BM extract orally for next 7 days. First subgroup (n=10) was given 40 mg/kg body weight, second subgroup (n=10) was administered with 80 mg/kg body weight and the third subgroup (n=10) was given 120 mg/kg body weight of BM extract (Fig.2).

Recovery group II, treated with Fluoxetine hydrochloride (FLX) (n = 10): exposed to foot shocks daily for 21 days and received daily intra-peritoneal (i.p.) injections of fluoxetine hydrochloride (FLX) with 10 mg/kg body weight for consecutive 7 days.

2.2. Stress Procedure

The foot shock chamber consists of a box containing an animal space positioned on a metallic grid floor connected to a shock generator and scrambler. Rats in stress group were placed in a box and received 60 inescapable foot shocks (0.8 mA intensity and 15 s duration with interval of 45 s) with randomized starting time (between 9:00 and 17:00 hours) and intervals during a 30 to 120

Somoday Hazra et al.
Evaluation of Antidepressant activity of *Bacopa monnieri* in rat: A study in Animal Model of Depression,
Drug discovery, 2012, 2(4), 8-13,

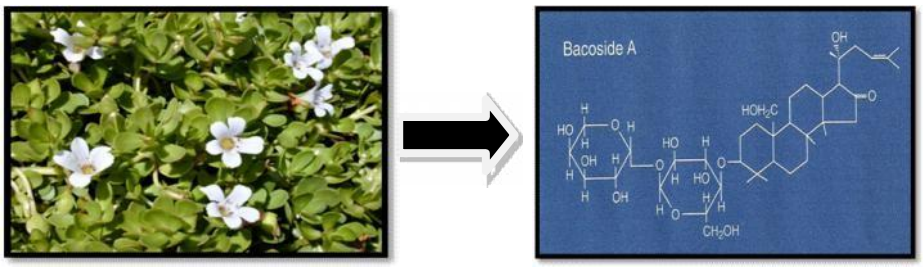

Figure 2

Bacopa monnieri plant with organic structure of its main component Bacoside A

Learned helplessness: Learned helplessness is a technical term that refers to the condition of a human or animal that has learned to behave helplessly, failing to respond even though there are opportunities for it to help itself by avoiding unpleasant circumstances or by gaining positive rewards. Learned helplessness theory is the view that clinical depression and related mental illnesses may result from a perceived absence of control over the outcome of a situation. Organisms which have been ineffective and less sensitive in determining the consequences of their behavior are defined as having acquired learned helplessness.

min session to make the procedure as unpredictable as possible. On last day rats were sacrificed using isoflurane anesthesia.

2.3. Shuttle Box Testing

Shuttle box sessions were run by PC computer with custom software developed for the system (TSE Active Avoidance Systems GmbH, Bad Hamburg, Germany. At the start of each shuttle box session, animals were exposed to a 5 min habituation period in the same chamber where inescapable shock (IS) or escapable shock (ES) was applied. This was followed by 30 escape trials in which the arch door separating the two halves of the shuttle box opened 5 s prior to the shock onset followed by randomized foot shocks delivered at an intensity of 0.6 mA for 30 s duration of escape latency (Shirayama et al., 2002). The test consisted of five fixed-ratio 1 (FR-1) trials during which one shuttle-crossing terminated shock. FR-1 trials were used to determine the normal motor function of the rats. For escape testing, FR-1 trials were followed by 25 trials during which the rat had to cross from one side of the shuttle-box to the other, and then return, to terminate the shock (fixed-ratio 2 or FR-2 trials). Shock terminated automatically if the response requirement was not met within 30 s of the shock onset. A mean latency for the 25 FR-2 trials of ≥ 20 s is defined as learned helpless (LH) while mean latency of < 20 s is classified as non-learned helpless (NLH). Both FR-1 and FR-2 trials were presented with an average inter-trial interval of 60 s. Crosses were automatically stored by the PC whenever a micro-switch was activated by tilting of the pivoted grid floor after the crossing event. Shuttle box escape test was performed under red light conditions between 9:00 and 13:00 hours during the active period of animals at least 1 h after the last stress session and before the stress procedure of that day. The escape test was performed five times (day1, 21, 28, 29 and 30) during the entire 30 days stress paradigm.

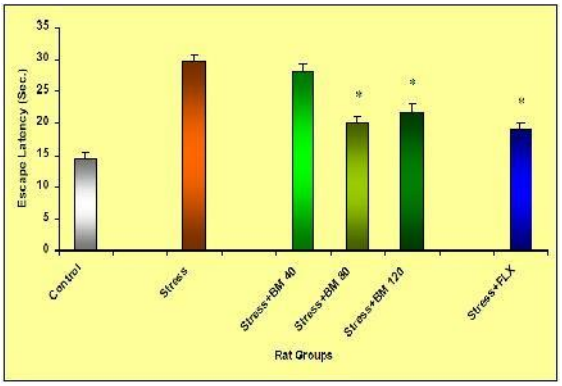

Figure 3

FR-2 Escape Latencies of the Rats of 4 Experimental Groups. BM treated group is subdivided into 3 subgroups. Escape latency is significantly reduced among BM 80, BM 120 and FLX treated group compared to Stress group rat (t_{BM80}= 4.97; df= 39; *p<0.001; t_{BM120}= 5.31; df= 39; *p<0.001; t_{FLX}= 5.37; df= 39; *p<0.001).

2.4. Administration of BM

We collected BM Extract (≥40% w/w) from Natural Remedies Pvt. Ltd., Bangalore, India and prepared the solution by dissolving 450 mg of dried powder in 80 ml distilled water and used for the study (Paulose et al., 2008) and administered orally to the rat once daily with the help of a specially designed feeding needle for next 7 days (from day 22 to day 28). Control group of animals received saline water. BM was administered at the same time on each day (8 a.m.–9 a.m.). Experiments were conducted after one hour of last dose of BM administration (day 28, day 29 and 30).

2.5. Administration of FLX

Fluoxetine hydrochloride (Sigma Aldrich, St. Louis, MI, USA) was dissolved in 0.9% physiological saline and injected intraperitoneally (i. p.) at the dose of 10 mg/kg body weight of the rats. The dosage of FLX was based on studies demonstrating a reversal of shuttle box escape deficits, after injections of FLX or exposure to chronic unpredictable shock. Antidepressant drug was administered from day 22 to day 28 once per day (Banerjee et al., 2012a). Experiments were conducted after one hour of last dose of FLX administration (day 28, day 29 and 30).

2.6. Determination of Plasma Corticosterone levels

Plasma corticosterone levels were measured in all four groups of rat: Control, Stress, graded doses of Bacopa treated recovery group I and FLX treated positive control group II. Blood samples were collected after sacrificing the animals and centrifuge immediately at 2000g at 4ºC for 15 min. Corticisterone levels were measured using commercially available Radioimmunoassay kit (ICN Biomedical, Costa Mesa, CA, USA).

3. RESULTS AND DISCUSSION

The mean FR-2 escape latencies were significantly higher ($F_{4,195}$ = 15.71; p < 0.05; Fig.3) in the stress group compared to normal controls,

Somoday Hazra et al.
Evaluation of Antidepressant activity of *Bacopa monnieri* in rat: A study in Animal Model of Depression,
Drug discovery, 2012, 2(4), 8-13,

LH Model of Behavioral Depression: The learned helplessness model (LH), one of the well validated animal models, is the best replicated one. The rationale is that exposure to uncontrollable and stressful life events makes people to feel like losing control, and sometimes leads to a depressive like behavior. The model is based on the observation that animals also develop deficits in escape, cognitive and rewarded behaviors when they have been subjected to repeated unavoidable and uncontrollable shocks. LH is induced in one day or over several days of repeated inescapable stress by the treating of tail or foot shock in shuttle boxes.

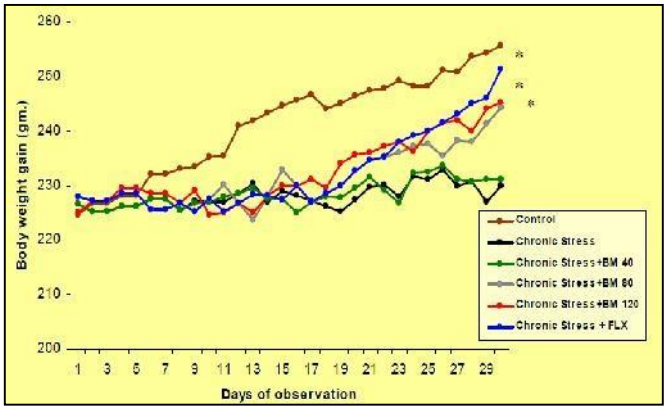

Figure 5

Representation of daily body weight gain among the 4 Experimental Groups. BM treated group is subdivided into 3 subgroups. Body weight is significantly restored among BM 80, BM 120 and FLX treated rats compared to Stress group rat (t_{BM80}= 3.92; df= 29; *p<0.001; t_{BM120}= 4.5; df= 29; *p<0.001 and t_{FLX}= 3.72; df= 29; *p<0.001).

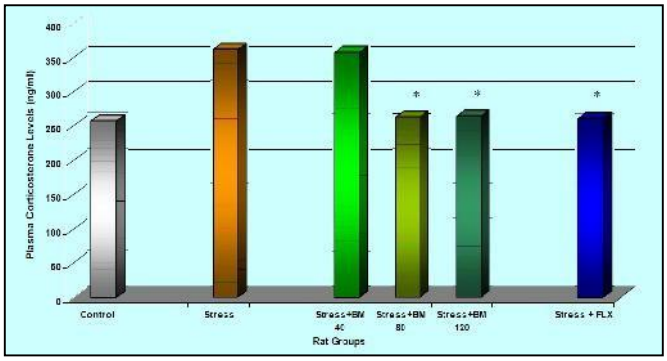

Figure 6

Representation of Plasma Corticosterone levels among the 4 Experimental rat groups. BM treated group is subdivided into 3 subgroups. Plasma Corticosterone level significantly reduced among BM 80, BM 120 and FLX treated rats compared to Stress group rat (t_{BM80}= 24.28; df= 9; *p<0.001; t_{BM120}= 29.84; df= 9; *p<0.001; and t_{FLX}= 39.84; df= 9; *p<0.001).

BM and FLX treated recovery groups. BM showed significant anti-depressant activity in the most commonly used paradigms of stress induced animal model depression LH. During the shuttle box escape test, 80 and 120 mg/kg body weight doses of BM significantly reduced escape latency compared to stress group rats (t_{BM80}= 4.97; df= 39; p<0.001; Fig.3 and t_{BM120}= 5.31; df= 39; p<0.001; Fig.3) suggesting anti-depressant activity and the activity was comparable to the reference drug FLX (t_{FLX}= 5.37; df= 39; p<0.001; Fig.3). Whereas 40mg/kg body weight dose of BM showed no significant change in escape latency compared to stress group rats (t_{BM40} =0.72; df= 39; p>0.05; Fig.3).

This is thought to reflect either a failure to persist in escape directed behavior after persistent stress or the development of passive behavior that disengages the animal from active forms of coping with stressful stimuli (Lucki, 1997). In learned helplessness test, rodents exposed to inescapable and unpredictable electric shock, at one situation fail to escape even when escape is possible. This is termed as escape failures. Potential anti-depressant drugs proved decreased escape failures (Banerjee et al., 2012a). The animals are also able to avoid the impending danger by escaping to the safe chamber, which is termed as avoidance responses, which are concomitantly increased. BM and FLX both significantly decreased escape failures and increased avoidance responses indicating anti-depressant activity. Escape failures and avoidance responses altogether are represented as escape frequency. After BM administration, escape frequency of BM 80 and BM 120 treated group rats showed significant increase of escape frequency compared to stress group rats (t_{BM80} =4.02; df= 39; p<0.001; Fig.4 and t_{BM120} =3.98; df= 39; p<0.001; Fig.4). There is no significant alterations in escape frequency of BM 40 treated rats (t_{BM40} =0.42; df= 39; p>0.05; Fig.4) compared to stress group rats.

Body weight gain was significantly affected by 21 days stress procedure. In recovery groups after withdrawal of stress exposure, graded doses of BM and FLX were administered. BM 80 and BM 120 treated rats restored their significant body weight along with FLX treated rat groups compared to chronic stress group rats (t_{BM80}= 3.92; df= 29; p<0.001; Fig.5 and t_{BM120}= 4.5; df= 29; p<0.001; Fig.5 and t_{FLX}= 3.72; df= 29; p<0.001; Fig.5). Statistical analysis clearly exhibited that there was no significant variation among BM 80, BM 120 and FLX administered rats ($F_{2, 87}$ = 0.29; p > 0.05; Fig.5). Loss of Body weight, the well established physiological marker of depression and the restoration of body weight through antidepressant drug treatment were elucidated by several scientists (Banerjee et al., 2012b). From our experiment, the significant weight gain among the BM 80 and BM 120 rat groups clearly forecast the antidepressant property of Bacopa. Administration of BM 40 dose showed no significant alteration on rats' body weight compared to stress group individuals (t_{BM40}= 1.43; df= 29; p= 0.08; Fig.5).

Plasma corticosterone levels (ng/ml) were measured in all four groups of rats and were as follows: Control group rats: 254.8; Stress group rats: 359.85; BM 40 treated group rats: 355.42; BM 80 treated group rats: 260.71; BM 120 treated group rats: 262.81 and FLX treated group rats: 259.38. Plasma corticosterone levels did not differ among Control, BM 80, BM 120 and FLX treated rats ($F_{3,36}$ = 0.86; p > 0.05; Fig.6). Similarly there is no alteration in plasma corticosterone levels among stress group and BM 40 treated group

Somoday Hazra et al.
Evaluation of Antidepressant activity of *Bacopa monnieri* in rat: A study in Animal Model of Depression,
Drug discovery, 2012, 2(4), 8-13,

($F_{1,18}$ =0.80; p > 0.05; Fig.6; t_{BM40}= 0.90; df= 9; p=0.19; Fig.6). After administration of BM 80, BM 120 and FLX, plasma corticosterone levels showed significant reduction compared to stress group rats (t_{BM80}= 24.28; df= 9; p<0.001; Fig.6 and t_{BM120}= 29.84; df= 9; p<0.001; Fig.6 and t_{FLX}= 39.84; df= 9; p<0.001; Fig.6).

4. CONCLUSION

In conclusion, to our knowledge, this is the first study that examines the effect of *Bacopa monnieri* in graded doses as antidepressant drug to the LH model of stress induced behavioral depression. Our study demonstrates diminished activation of avoidance response during shuttle box escape test among the LH rats which can be restored by acute treatment with BM 80 and BM 120. Similarly these doses have the capability to reduce plasma corticosterone levels significantly along with the significant restoration of animal's body weight. Our present study clearly elucidates the antidepressant properties of our experimental herbal product BM. Our study not only suggests the antidepressant property of *Bacopa monnieri* but also raises actual admissible dose of it required for recovery from depression and other stress-related psychiatric disorders.

SUMMARY OF RESEARCH

1. Restoration of avoidance response among the LH rats due to acute treatment of *Bacopa monnieri*, which clearly corroborates the property of well established reference antidepressant drug Fluoxetine hydrochloride.
2. Significant restoration of body weight of animal through acute administration of BM 80 and BM 120
3. Significant reduction of plasma corticosterone levels after acute treatment with BM (BM 80 and BM 120) clearly coincide with FLX treated corticosterone level.

FUTURE ISSUES

1. Evaluation of *Bacopa monnieri* as antidepressant drug to decipher the signaling cascade in stress related neuropsychiatric disorders in animal model of depression.

DISCLOSURE STATEMENT

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Somoday Hazra et al.
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Somoday Hazra et al.
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Drug discovery, 2012, 2(4), 8-13,