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Antidepressant-like Potentials of *Buchholzia Coriacea* Seed Extract: Involvement of Monoaminergic and Cholinergic Systems, and Neuronal Density in the Hippocampus of Adult Mice

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Summary: *Buchholzia coriacea*, taken by elderly, has phytochemicals that have neuro-active metabolites, and the folklore documented its use in neuro-behavioral despairs. Previous study in our laboratory shows that methanol extracts of *Buchholzia coriacea* (MEBC) seeds possess antidepressant-like potentials in laboratory rodents. This present study was conducted to investigate the probable mechanism(s) of action by which MEBC potentiates its effects using laboratory rodents. Involvements of serotonergic, cholinergic and adrenergic systems were studied using Forced Swimming Test (FST) and Tail Suspension Test (TST) models of behavioral despair. Antagonists which including: Prazosin, an alpha-1-adrenergic receptor blocker (62.5 µg/kg, i.p.), metergoline, a 5HT2 receptor blocker (4 mg/kg, i.p.) and atropine, a -muscarinic cholinergic receptor blocker (1mg/kg i.p.) were administered before effective dose of MEBC (50mg/kg). Also, the hippocampi of the animals were studied for changes in neuronal density using Nissl Staining. Our findings showed that mobility was reversed in animals pre-treated with atropine, prazosin, and metergoline significantly ($P<0.05$), showing a possible involvement of the corresponding systems. However, there was a significant reduction in immobility time ($P<0.001$) during FST after chronic administration of the MEBC. The hippocampus showed no significant changes ($P<0.05$) in neuronal density. In conclusion, MEBC probably potentiates its antidepressant-like potentials via the cholinergic, adrenergic and partly by serotonergic systems.

Keywords*: Buchholzia coriacea*, Serotonergic system, Cholinergic system, Adrenergic system

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INTRODUCTION

Mood disorders like major depression and bipolar disorders are mostly common psychiatric disorders in modern society. About 1% and 16% of the population are estimated to be affected by bipolar disorder and major depression one or more times during their life time, respectively (Kessler *et al*., 2005). In Nigeria alone, about 3.1% of the population has been estimated to be having depression (Gureje *et al.*, 2010). The presence of the common symptoms of these disorders are collectively called 'depressive syndrome' and includes a long-lasting depressed mood, feelings of guilt, anxiety, and recurrent thoughts of death and suicide (Nestler *et al*., 2002). It has been estimated that the genetic contribution to the manifestation of depression is between 40-50% (Fava *et al*., 2000). Further studies carried out extensively have led to a variety of hypotheses for the molecular mechanism of depression, but no definite or specific pathogenic mechanism has been reported.

Many years ago, before the advent of the modern drugs for treating psychiatric conditions, it was discovered that some patients could receive significant relief from severe psychotic depression through severing the neuronal connections between the prefrontal areas of the brain by a method called prefrontal lobectomy. About two-thirds of the depressed patients respond to the currently available therapies but the magnitude of improvement is still disappointing. Therefore, the need for newer, better-tolerated and more efficacious treatments remains the major pharmacological interest and pursuit. Therapists from different regions of the world have used herbal medicines to alleviate affective disorders for many decades. In addition, the search for novel pharmacotherapy from medicinal plants for psychiatric illnesses has progressed significantly in the past years (Zhang, 2004). An increasing number of herbal products have been introduced into psychiatric practice, as complementary or alternative medicines, and also there are a large number of herbal medicines whose therapeutic potentials have been assessed in a variety of experimental animal models (Zhang, 2004). In fact, these models have contributed to the screening of new psycho pharmacological tools and to the understanding of their biological activities (Buller and Legrand, 2001). The plant *Buchholzia coriacea*

(*Capparidaceae*), known as wonder plant (musk tree) of which the seeds are called wonderful kola, has won for itself some folkloric importance as local abortifacients, ecbolic (promoting labor by increasing uterine contractions), vermifages, wound and snake bite treatments. Scientifically, it is known for its therapeutic effects as antimicrobial and antihelminthic potentials (Ajaiyeoba *et al*., 2003), hypoglycemic activities (Adisa *et al*., 2010), antibacterial activities (Mbata *et al*., 2009), anti-inflammatory, analgesic and antipyretic activities (Enechi *et al*., 2006; Onasanwo *et al.,* 2013); anthelminthic activities (Nweze *et al*., 2006). Onasanwo and co-workers showed that methanol extract of *Buchholzia coriacea* has antidepressant-like properties in laboratory mice (Onasanwo *et al*., 2013). However, the mechanisms of potentiation are not yet elucidated. The 'monoamine hypothesis,' which suggests a deficiency or imbalances in the monoamine neurotransmitters, such as serotonin, dopamine and norepinephrine, as the cause of depression, has been the central topic of depression research for the last five decades. This hypothesis has been initiated and supported by the fact that early versions of antidepressants including monoamine oxidase and tricyclics inhibitors have the common effect of acutely enhancing monoamine function (Ressler *et al*., 2000; Manji *et al*., 2001; Morilak *et al*., 2004). Recently, research update has shown that the mode of action of antidepressants is through hippocampal neurogenesis, which is referred to as the production of new neurons in the brain. The process of adult neurogenesis is located in two discrete brain regions: the sub-ventricular zone (SVZ) and sub-granular zone (SGZ) of dentate gyrus of the hippocampus of the brain. The heterogeneous nature of depression suggests an involvement of multiple distinct brain regions, which may be responsible for the diverse symptoms. This hypothesis human imaging and post-mortem studies of the brain have supported, implicating brain areas including the prefrontal and cingulate cortex, hippocampus, ventral striatum, amygdala, and thalamus (Drevets *et al*., 2002). Together, these brain regions operate a series of highly interacting circuits that forms a neural circuitry involved in depression (Nestler *et al*., 2002). The hippocampus is one of several limbic structures that have been extensively studied in individuals with psychiatric and neurologic disorders in the last decade (Nestler *et al*., 2002; Eisch *et al*., 2008). Apart from its critical role in learning and memory, the hippocampus is one of the only two areas in mammalian brain where adult neurogenesis is evidenced (Eisch *et al*., 2008). Therefore, the main objective of this research work is to evaluate the possible mechanisms by which *Buchholzia coriacea* seeds potentiate its antidepressant activities using laboratory rodents, with focus on the monoaminergic system and hippocampal neuronal density.

MATERIALS AND METHODS

Animals

Female mice (20g - 23g) obtained from Central Animal House, University of Ibadan, Ibadan,
Nigeria were used in the study. Each mouse was used once in the study. The animals were caged at room temperature, with 12-hour light-dark cycle. The animals were allowed free access to water, and standard diet was given *ad libitum*.

Plant material and extraction procedure

The *Buchholzia coriacea* seeds were purchased locally from Oje market, Ibadan, Nigeria, and identified at the Botany Department, University of Ibadan, Ibadan, Nigeria. Although, the plant had been authenticated at the herbarium of Forestry Research Institute of Nigeria (FRIN), Ibadan, Oyo State, Nigeria and a voucher specimen was already there. The outer coats of the seeds were peeled off until a purple color was left. They were washed clean with distilled water to remove adhering particles after which they were sliced and properly shade- dried, then pulverized. The powdered seeds were macerated in aqueous methanol (80%v/v) for a total of 15days (solvent was replaced every five days) with daily shaking. The extract obtained was concentrated to a dark-brown residue on a rotary evaporator at 40oC and weighed. The methanol extract of *Buchholzia coriacea* seeds (MEBC) obtained was concentrated to dryness by lyophilization and stored in the refrigerator until needed for analysis.

Drugs and treatment regimen

To assess the involvement of the monoaminergic systems in the antidepressant-like effect of
Methanol Extract of *Buchholzia Coriacea* (MEBC); mice were pre-treated with metergoline (4mg/kg, i.p.), a non-selective 5-HT2 receptor antagonist, at a dose effective in blocking the *in vivo* effect induced by 5-HT2 receptor agonists in mice, prazosin (62.5µg/kg, *i.p*.), an alpha-1-adrenoceptor antagonist, atropine (1mg/kg, *i.p*.), a muscarinic cholinergic receptor antagonist. The test for elucidation of mechanisms made use of 6 groups of 6 mice per group. Group 1 was control and received vehicle only. Group 2 was treated with 50mg/kg MEBC only while Groups 3 to 5 were pretreated with above named antagonist 15minutes before administration of 50mg/kg MEBC, after which they were subjected to the behavioral tests of either forced swimming test or tail suspension test. Group 6 received imipramine (60mg/kg) only, which serves as the standard group.

Neuro-behavioral study-depression models

i. Forced Swimming Test (FST): The forced swim test (FST) has been considered to be the most widely used

pharmacological *in-vivo* model for assessing antidepressant activity (Porsolt *et al.*, 1978). The set-up consists of a clear plexiglass cylinder (20cm high by 12cm diameter) filled with water to a 15cm depth. Water used during the experiment was kept at a temperature (34 ± 1^{o}C).

ii. Tail Suspension Test (TST): The tail suspension test (TST) was performed as earlier described (Steru *et al*, 1985). The mice were individually suspended at 60cm above the surface of the floor with an adhesive tape placed 1cm away from the tip of the tail. Immobility duration was recorded for the last 5minutes after 1 minute of acclimatization during the 6minutes test. Mice were considered immobile when they hung passively and were completely motionless.

Evaluation of the Involvement of Adult Hippocampal Neuronal Density

In each group, animals were classified into two (2) subgroups: one for behavioral studies and other for histological studies. Forced swimming test (FST) was used to assess the behavioural activity. Animals were pretreated with either vehicle or MEBC for 7, 14 or 21days. At the end of their respective days of pre-treatment, animals either undergo forced swimming test or was sacrificed and brain harvested for nissl staining.

Brain harvest and staining: Animals were anaesthetized using ketamine (80mg/kg).
Immediately after the animal lost its righting reflexes, mouse was laid on its back and the thorax was opened carefully to avoid bleeding. Animals were perfused intracardially with normal saline followed by 4% Phosphate-Buffered Formalin (PBF). After proper fixation, the animal skull was cut-open; brain removed and preserved in a glass tube containing 4% PBF for 72hours before slide preparation. Brain tissues were further processed into paraffin blocks and 40µm section were cut and made into slides for Nissl staining. Tissues were stained in 0.1% Cresyl violet.
Number of neuronal cells in the granular zones of the hippocampi was counted per square millimeter, to calculate the neuronal densities.

Statistical Analysis

The results obtained were expressed as mean ± S.E.M. Variance was analyzed using One-way Analysis of Variance (ANOVA), followed by Newman–Keuls' multiple comparisons test. P<0.05 was considered to be statistically significant.

RESULTS

Involvement of the monoaminergic system in antidepressant-like activities of Methanol Extract of *Buchholzia coriacea* (MEBC) in Forced Swimming Test.

On Immobility**:** As shown in figure 1a, 50mg/kg of MEBC significantly reduced immobility (P<0.05) in comparison with control. However, pre-treatment with antagonists Prazosin, an alpha1-adrenergic receptor blocker (62.5 µg/kg, i.p.), metergoline, a 5HT2 receptor blocker (4mg/kg, i.p.) and atropine, a muscarinic cholinergic receptor blocker (1mg/kg, i.p.) reversed decreased immobility as seen with group treated with 50mg/kg of MEBC. Imipramine (60mg/kg) significantly reduced immobility (P< 0.001) when compared to the control group.

On swimming: As shown in figure 1b, MEBC (50mg/kg) and metergoline (pre-treated) groups also show a significant increase (P<0.001) when compared with control. Animals pre-treated with atropine and prazosin showed a significant decrease in swimming activity (P<0.01 and P<0.05 respectively) when compared to the animals that were treated with MEBC (50mg/kg) only. However, there was no significant decrease in animal pre-treated with metergoline when compared to the group that received MEBC (50mg/kg) only.

On Climbing: as shown in figure 1c, MEBC (50mg/kg) and imipramine treated groups showed increase in climbing time (P<0.001) when compared with animals treated with vehicle. Also there was a significant increase in climbing time atropine and Prazosin (P<0.001 and P<0.05, respectively) when compared to groups treated with MEBC (50mg/kg) only. In contrast, there was a significant reduction in climbing time in animals pre-treated with metergoline when compared to animals that received MEBC (50mg/kg) only

Involvement of the monoaminergic and cholinergic systems in antidepressant-like activities of Methanol Extract of *Buchholzia coriacea* (MEBC) in Tail Suspension Test.

As shown in figure 2, imipramine significantly reduced immobility (***P<0.001) when compared to control. There is also a significant reduction in immobility (*P<0.05) in animals treated with MEBC (50mg/kg). However, there was a reversal in mobility in animals pre-treated with antagonist when compared with animals treated with MEBC (50mg/kg) only.

Involvement of chronic administration of Methanol Extract of *Buchholzia coriacea* (MEBC) on immobility and Adult Hippocampal Neuronal Density.

On immobility: As shown in figure 3, all groups pre-treated for 7, 14 or 21 days shows a significant reduction in immobility (P<0.001) when compared with their respective control (vehicle) groups.

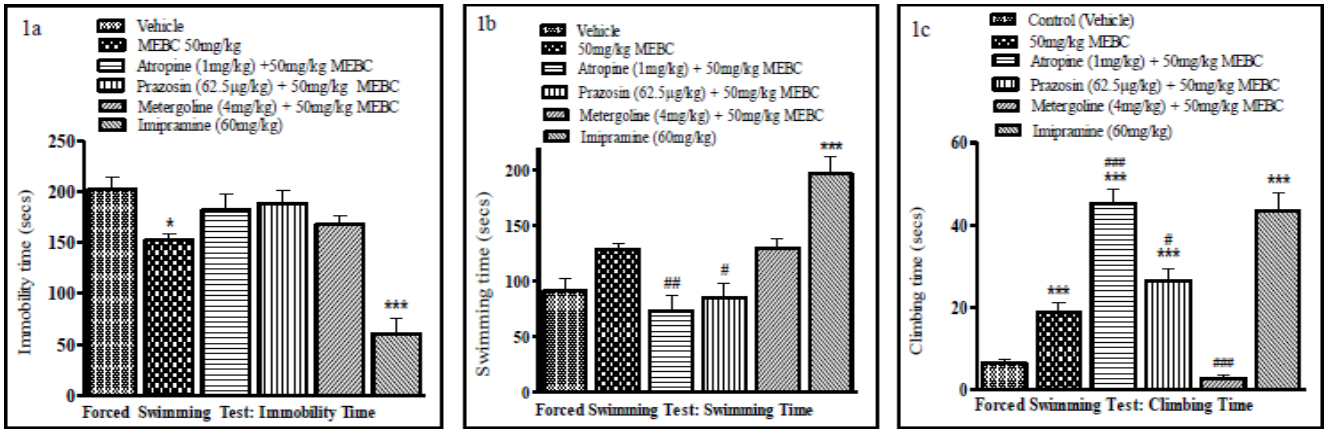

Figure 1. Effect of MEBC, monoamine antagonist, atropine and imipramine on (a)immobility, (b)swimming and (c)climbing times in forced swimming test. Values were expressed as mean ± S.E.M, ***P<0.001, *P<0.05 versus control; (Fig. 1b&1c) ###P<0.001,##P<0.01,#P<0.05 when compared with50mg/kg MEBC treated group, using one way ANOVA followed by Newman-Keuls post-hoc multiple comparison test. (n=6).

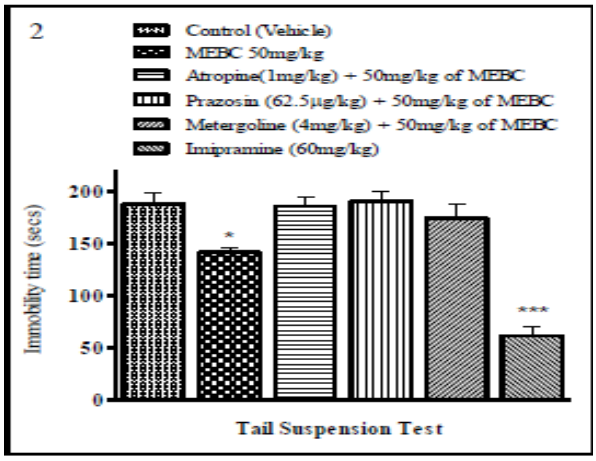

Figure 2**.** Effect of MEBC, monoamine antagonist, atropine and imipramine on immobility time in tail suspension test. Values were expressed as mean ± S.E.M, ***P<0.001, *P<0.05 versus control; using one way ANOVA followed by Newman-Keuls post-hoc multiple comparison test. (n=6).

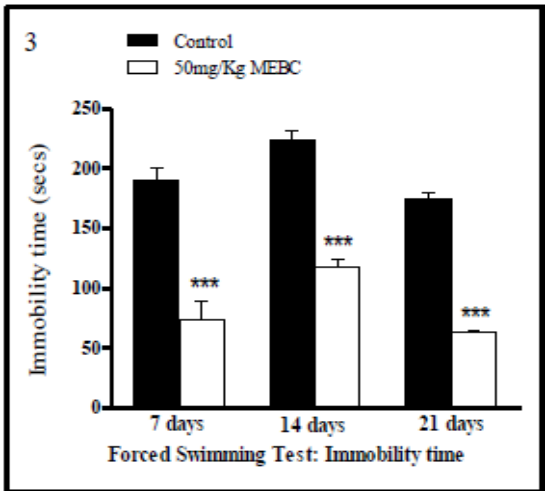

Figure 3. Effect of Methanol Extract of *Buchholzia coriacea* on immobility time in forced swimming test. Values were expressed as mean ± S.E.M, significant decrease ***P<0.001 versus controls; using one way ANOVA followed by Newman-Keuls post-hoc multiple comparison test. (n=6).

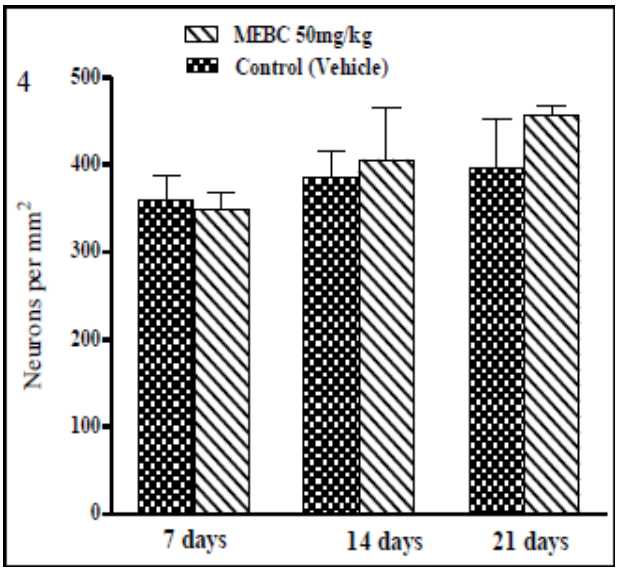

Figure 4. Number of Nissl stained granule neurons per mm2 in granular zone of the dentate gyri of the hippocampi of animals pretreated with either vehicle (10ml/kg) or MEBC (50mg/kg). Values were expressed as mean ± S.E.M.

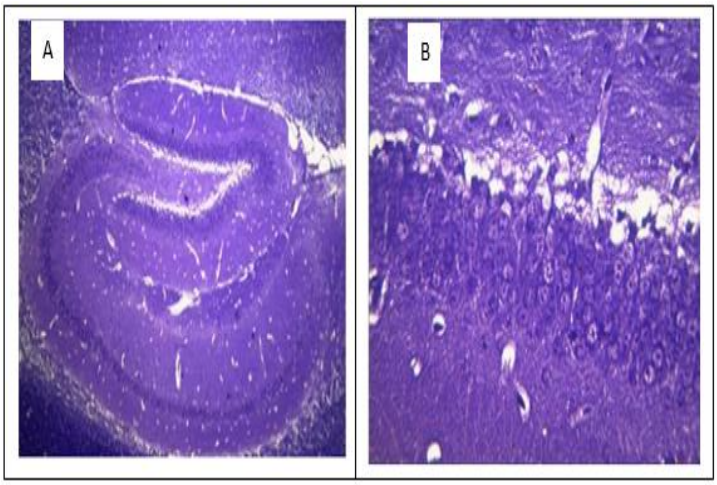

Plate1. Photomicrographs of hippocampus of animals showing positive staining with nissl. (A. Mag. X40, B. Mag. X400)

On Adult Hippocampal Neuronal Density: As shown in figure 4, there was no significant difference ($P<0.05$) in hippocampal neuronal density within the groups treated with either vehicle (10ml/kg) or MEBC (50mg/kg) for 7, 14 or 21 days

DISCUSSION

The pathophysiology of depression is linked to the deficiency of one or more monoamines in affected persons. Antidepressants demonstrated their effects by regulating synaptic levels of one or more monoamines (Elhwuegi, 2004). Hence, this study explored the impact of monoaminergic and cholinergic antagonists on the antidepressant-like effect of the methanol extract of *Buchholzia coriacea* (MEBC). Forced Swimming Test (FST) and Tail Suspension Test (TST) were used as the tests in mechanistic studies due to its increased sensitivity (Cryan *et al*., 2002; 2005a; 2005b). The modified Porsolt forced swimming test has been suggested to have good sensitivity for detecting the effects of antidepressants in rodents and other laboratory animals (Cryan *et al*., 2005). This test involves measuring the immobility, swimming behavior and climbing behavior of rodents upon subsequent exposure to swimming.

On serotoninergic system**,** several studies had established the role of serotonin in depression (Kennett *et al.,* 1987; Elhwuegi, 2004; Tatarczynska *et al*., 2004). Our earlier study showed that MEBC (50mg/kg) reduced immobility in laboratory mice (Onasanwo *et al.,* 2013) which suggests its antidepressant activities. MEBC increased swimming and reduced immobility behavior suggesting an involvement of 5-hydroxytryptaminergic (5-HT) neurotransmission in its antidepressant-like activity. However, this immobility was reversed when metergoline, a nonselective 5HT2 receptor antagonist was administered to the animals before treatment with MEBC. Also, there was a significant increase in swimming activities after treatment with metergoline, Therefore, it may be possible that MEBC produces its antidepressant-like effect through interaction with other serotonergic receptor sub-types.

Analyses of antidepressant drugs in the forced swimming test allow discrimination in between serotonergic drugs (e.g., fluoxetine) that reduced immobility by increasing swimming (Detke *et al*., 1995; Rénéric *et al*., 1998). The enhancement of swimming activity and reduction of immobility in mice that was comparable to that observed after the acute administration of imipramine suggest an antidepressant-like effect of the extract.

On adrenergic system**,** the alpha-1-adrenoceptor has been shown to underlie some of the antidepressant-like responses of drugs in behavioural models of depression (Danysz *et al*., 1986; Cardoso *et al*., 2009). Imipramine increased the climbing activity in this experiment, suggesting a mechanism that involves noradrenergic neurotransmission (Detke *et al*., 1995). Pre-treatment with Prazosin (62.5μg/kg), an alpha-1-adrenergic receptor antagonist reversed the immobility that was observed when MEBC (50mg/kg) was administered alone; both in forced swimming test and tail suspension test paradigms. This result indicates that MEBC may exert its effect in the FST and TST paradigms, by interacting with alpha1-adrenoceptors. Moreover, the blockade of α-1-adrenoceptors mimics depressive states, which, like chronic stress, are associated with α1-adrenoceptor desensitization (Stone *et al*., 2003). In contrast, chronic antidepressants and electroconvulsive therapy enhance the density and functional activity of α-1-adrenoceptors in structures such as frontal cortex and hippocampus (Stone *et al*., 2003; Cardoso *et al*., 2009).

On cholinergic system, pre-treatment with atropine reduced swimming activity which signifies a possible inhibition of cholinergic pathways in mood regulating centers. The hippocampus which is rich in cholinergic neurons and other trajectories to other part of the CNS e.g. prefrontal cortex, suprachiasmatic nucleus and amygdala is also very important in mood regulation. So, the blockade of muscarinic cholinergic pathway may produce possible depressive behaviors in animals, as increased swimming activity is corresponding to anti-depressant activities.

The involvement of hippocampal neuronal density was also studied here. Efficacy of antidepressants has been suggested to be linked to production of new neurons especially in the hippocampus of the brain (Malberg *et al*., 2000; Santarelli *et al*., 2003). Chronic administration of MEBC significantly reduced immobility after 7, 14 and 21 days of pre-treatment when tested using FST, which may suggest the strengthening of neuronal circuitry involved in mood regulation.

In this study, we observed that there was no significant increase in neuronal density in the different pre-treated groups of animals. This could be as a result of the time required for the action of antidepressants, which generally take weeks. However there may be presence of proliferating cells in the hippocampus, but have not differentiated into mature neurons, specific technique like immunohistochemistry targeting these proliferating cells would help in identifying them. (Malberg *et al*., 2000; Santarelli *et al*., 2003). Different animals were used for the behavioral and histological studies, because it has been shown that both acute and chronic stress suppressed neurogenesis of dentate gyrus granule neurons (Baune *et al.,* 2006; Hihn *et al.,* 2006).

This allow for proper physiological examination of the therapeutic effect of the MEBC without any prior influence of stress-induced neuronal loss, which they

would have been exposed to if the same animals were used for histology after successive swimming tests.

In the brain, many circuitries are involved in mood regulation and this information is transferred by synapses between neuronal cells. Depression has been suggested to be associated with loss of neurons especially in the hippocampus which account for low hippocampal volume. Also, it has been suggested that antidepressants stimulate the expression of neurotrophic factors, increase the density, the length and the arborization of the dendrites (Magarinos *et al.*, 1999) and enhance the synaptic plasticity (Magarinos *et al.*, 1999; Manji *et al.*, 2001; Hayley *et al.*, 2005).

In conclusion, antidepressant-like potential of methanol extract of *Buchholzia coriacea* may be mediated by cholinergic, adrenergic and partly by 5-HT2 systems.

Further studies will be to investigate the involvement of other monoaminergic systems like dopaminergic system. It will also be interesting to look into the involvement of the subtypes of the various monoaminergic receptors. Specific compound(s) will be isolated from the seeds of *Buchholzia coriacea*, in order to know which metabolite in the seeds of *Buchholzia coriacea* is responsible for the antidepressant-like activities. The role of Brain Derived Neurotrophic Factor (BDNF) will also be studied. Immunohistochemistry of hippocampal proliferating cells will be carried out, so as to be specific on the role of adult hippocampal neurogenesis in its potentiation of the antidepressant-like activities of MEBC

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