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BACOPAMONNIERA, A NOOTROPIC HERB ALLEVIATES ABNORMAL MOLECULAR AND IMMUNOHISTOCHEMICAL CHANGES EVOKED BY CHRONIC EXPOSURE OF METHYLMERCURY IN RAT CEREBELLUM

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ABSTRACT: Methylmercury (MeHg), a highly toxic environmental pollutant, induces oxidative stress and dysfunction in many cell types. *Bacopa monniera* is a perennial herb, and is used as a nerve tonic in ayurveda, a traditional medicinal system in India. This study was aimed to evaluate the effect of *Bacopa monniera* extract (BME) on MeHg-induced toxicity in rat cerebellum. Male Wistar rats were administered with MeHg orally at a dose of 5 mg/kg b.w. for 21 days. Experimentalrats were given MeHg and also administered with BME(40 mg/kg, orally) 1 h prior to the administration of MeHg for 21 days. After treatment MeHg induction caused increased level of Scgb3a1mRNA whereas the level was reduced by BME pretreatment. GPx4 expression was down regulated and HSP70 expression was up regulated in MeHg intoxicated group. Immunohistochemical changes were observed in TRxR1 and GFAP protein in MeHg induced group. BME pretreatment altered the expression of proteins and Immunohistochemical changes to near normal. These findings strongly implicate that BM has potential to protect brain from oxidative damage resulting from MeHg-induced neurotoxicity in rat.

INTRODUCTION: Methylmercury (MeHg) is a well-recognized environmental contaminant with established health risk to human beings by fish and marine mammal consumption. Oxidative stress is associated with the accumulation of high levels of reactive oxygen species (ROS), which has been implicated in MeHg-induced neurotoxicity both *in vivo* and *in vitro* [1, 2] and the impairment of cellular antioxidant defences [3, 4].

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Excessive ROS production may also induce the oxidation of membrane polyunsaturated fatty acids, leading to a decrease of mitochondrial membrane potential, yielding a multitude of lipid peroxidation products, depleting antioxidant defences, which in turn diminishes membrane permeability. The decrease of mitochondrial membrane permeability affects electron transference, which is associated to ROS production due to partial reduction of molecular oxygen [5]. Ultimately, the additive or synergistic mechanisms of cellular disruption caused by MeHg lead to cellular dysfunction and cell death.

The selenoproteins GPx and TrxR have been described as important antioxidant enzymes in the cellular protection against damage caused by ROS

[6]. These proteins are important components of the cellular antioxidant systems, and their inhibition contributes to the disruption of the normal redox balance of brain cells [7].

Bacopa monniera (Brahmi, family: Scorophulariaceae), a traditional Ayurvedic medicinal plant is a small creeping annual herb commonly growing in marshy places throughout India ascending to an altitude of 1320m. According to the indigenous system of medicine practised in India, the plant commonly known as Brahmi is claimed to be a potent nerve tonic, enhancing memory and improving mental function. It is extensively used for centuries for treatment of epilepsy, insomnia anxiety and also a mild sedative and memory enhancer [8, 9, 10]. Besides, *Bacopa monniera* displays antioxidant, antistress and anxiolytic properties in experimental animals[11, 12]. Further it improves the performance of rats in various learning situations such as shock-motivated brightness discrimination reaction, an active conditioned flight reaction, continous avoidance response[13]and attenuates experimentally induced amnesia in experimental animals [9, 14].

Several clinical studies have confirmed the beneficial actions of *Bacopa monniera*[15]and the pharmacological actions are mainly attributed to the saponin compounds present in the alcoholic extract of the plant. The major chemical constituents isolated and characterized from Bacopa are dammarane type of triterpenoidsaponins[16]. Several pharmacological [17, 18] and clinical studies [19, 20] on the extracts of *Bacopa monniera* standardized to the Bacosides A and B have been reported. Bacoside A is shown to alleviate the amnesic effects of scopolamine[15], protection against phenyotin-induced deficit in cognitive function in mice [21], protective against chronic exposure to cigarette smoke [22] and also against morphine induced oxidative stress in rats [23].

A previous study from our group has shown the protective effect of *Bacopa monniera* on MeHg induced oxidative stress, behavioural changes and mitochondrial dysfunction [24, 25, 26]. We have extended our study in activity of selenoprotein enzymes, expression of Scgb3A1 and immunohistochemical changes.

MATERIALS AND METHODS:

Chemicals:
Methylmercury chloride was purchased from Sigma Chemicals. All antibodies utilized in this study were purchased from Santa Cruz Biotechnology (Santa Cruz, CA, USA). All the other chemicals used in this work were from the highest analytical grade

Preparation of *Bacopa monniera* Extract:
The plant material was collected at Chennai, Tamil Nadu and will be authenticated by Dr. A. Sasikala, Captain Srinivasa Murthi Drug Research Institute for Ayurveda, Arumbakkam, Chennai, Tamil Nadu. The plant was shade dried and coarsely powdered plant material (1KG) was extracted with 90% ethanol in the cold (48 hrs). The extract was filtered and distilled on a cold water bath to obtain a dark green syrupy mass. It was finally dried in vacuum.

Animals:
Male Wistar Albino rats weighing 250-300g (age of 8-10 weeks) were obtained from Central Animal House, Dr. ALMPGIBMS, University of Madras, Taramani campus, Chennai-113, TamilNadu, India. Rats were housed separately in polypropylene cages and fed standard pellet diet (purchased from Hindustan Lever) kept under hygienic conditions. Rats were kept on a 12hr light and dark cycles with free access to water (RO water) *ad libitium*. All experiments and protocols described in the present study were approved by the Institutional Animal Ethics Committee (IEAC) of Dr. ALMPGIBMS, University of Madras, Taramani campus, Chennai-113, TamilNadu, India.

Rats were divided into four experimental groups of 6 animals each. Group I: control (vehicle orally), Group II: (5mg/kg, b.w) [27] orally for 21 days, Group III: MeHg+BME (40mg/kg b.w) orally 1 h prior to the administration of MeHg for 21 days, Group IV: BME alone (40mg/kg b.w) orally for 21 days. Experimental animals were handled according to the University and Institutional legislation, regulated by the Committee for the Purpose of Control and Supervision of Experimental on Animals(CPCSEA), Ministry of Environment and Forest (Animal welfare Division), Government of India (IAEC No. 01/07/2012).

Tissue preparation:
After treatment period, experimental animals and control animals were killed by cervical dislocation. Brains were immediately taken out and washed with ice cold saline to remove blood and kept at -80ºC. The cerebellum was rapidly dissected from the intact brain carefully on ice plate according to the stereotaxic atlas of Paxinos and Watson[28].

mRNA expression:
Total RNA was isolated from tissues was using Trizol method (Sigma Chemicals). First stand cDNA was synthesized using cDNA synthesis kit (Abcam). PCR was performed using the oligonucleotides for Scgb3a1. Sence: tctgtgtggctctgctcagt (5'-3'). Antisence: gatggccaagtggcttaatg (5'-3').

Western blotting:
The cerebellum was homogenized and Western blotting was performed. The proteins were separated by SDS-PAGE and transferred to nitrocellulose membranes. Membranes were incubated with specific primary antibodies for the determination of GPx4, HSP70, and β-actin protein expression.

Immunohistochemistry:
Immnuohistochemical analyses were performed using primary antibodies GFAP and TRxR1 (Santa Cruz biotechnology, Santa Cruz, USA).Universal secondary antibody. (Leica Biosystem)

RESULTS:

Effect of BME on MeHg induced alterations in the expression of Scgb3a1 protein in cerebellum of control and experimental rats:
The Scgb3a1 mRNA level was found to be increased (p<0.01) in MeHg induced group when compared to control. Pretreatment with BME significantly reduced (p<0.05) the expression of mRNA. BME alone treated rats resembles control **Fig.1.**

Fig. shows the effect of BME on mRNA expression of Scgb3a1 protein in cerebellum of MeHg induced control and experimental rats. DNA marker shown in Lane.5. Scgb3a1 expression was increased in MeHg induced group (Lane.2). BME pretreatment reduced the expression (Lane.3). In Lane 1 (control) there was no expression. BME alone similar as control (Lane.4). Data represents mean±SD of six rats in each group. Levels of mRNA were normalized to that of *GAPDHA*. Statistical significance (P value): $p<0.01$** significantly different from control group. $p<0.05$* different from MeHg induced group.

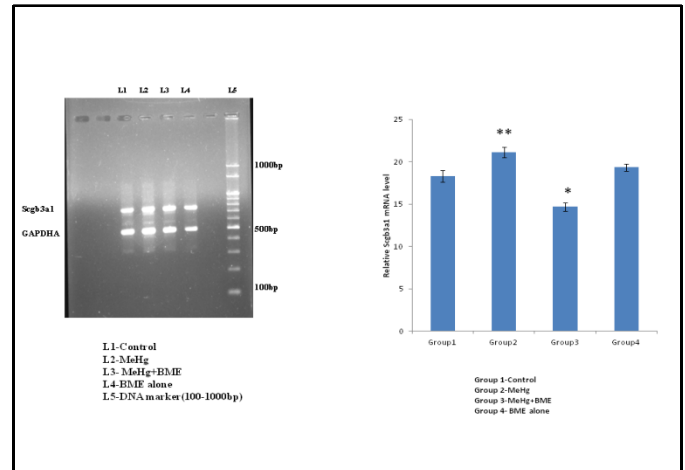

FIG.1

Activity of BME on MeHg induced expressions in GPx4 and HSP70 in cerebellum of control and experimental rat:
GPx4 and HSP70 protein expressions were analyzed by western blotting. GPx4 expression was down regulated (p<0.01) in MeHg intoxicated group when compared to control. Whereas the GPx4 expression was up regulated (p<0.01) by pretreatment with BME.BME alone group resembles like control.

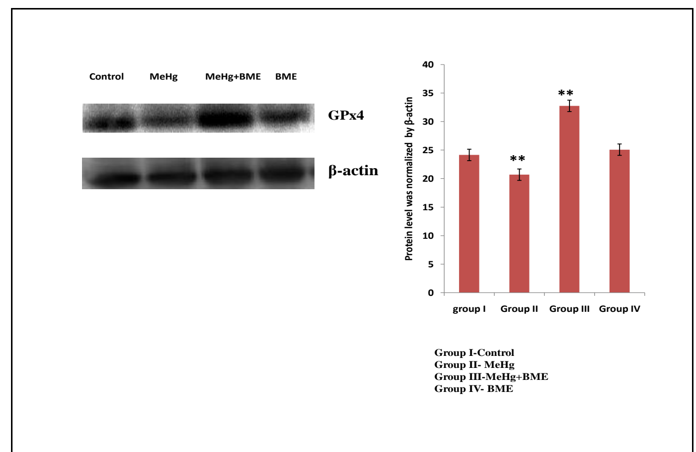

FIG.2

Fig. shows the immunoblot expression level of GPx4 and densitometric analysis of GPx4 immunoreactive bands. Statistical significance (P

value): $p<0.01$** significantly different from control group. $p<0.01$** different from MeHg induced group. Protein levels were normalized by β-actin immunocontent and expressed as a percentage of control.

Activity of BME on MeHg induced expressions in HSP70 in control and experimental rats:

HSP70 protein expression was up regulated ($p<0.01$) in MeHg induced group compared with control. While BME pretreatment, down regulated ($p<0.05$) the above expression. BME alone group similar as control.

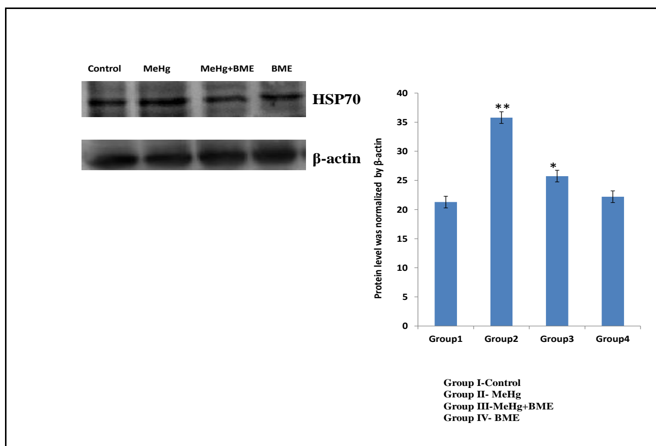

FIG.3

Figure shows the immunoblot expression level of HSP70 and densitometric analysis of HSP70 immunoreactive bands. Statistical significance (P value): $p<0.01$** significantly different from control group. $p<0.05$* different from MeHg induced group. Protein levels were normalized by β-actin immunocontent and expressed as a percentage of control.

Effect of BME on MeHg induced immunohistohemical changes in cerebellum of control and experimental rat:

We observed the immunohistochemical analysis of GFAP and TrxR1 protein. In control group TRxR1 expression was normal (**Fig.4a**). A significant decrease in the expression of TRxR1 in the granular cell layers was observed in MeHg intoxicated group when compared to control (**Fig.4b**).

A moderate decrease in the expression of TRxR1 was observed in BME pretreatment group (**Fig.4c**). BME pretreatment could not completely revert the condition.BME alone group resembles like control having normal expression of TRxR1 (**Fig.4d**).

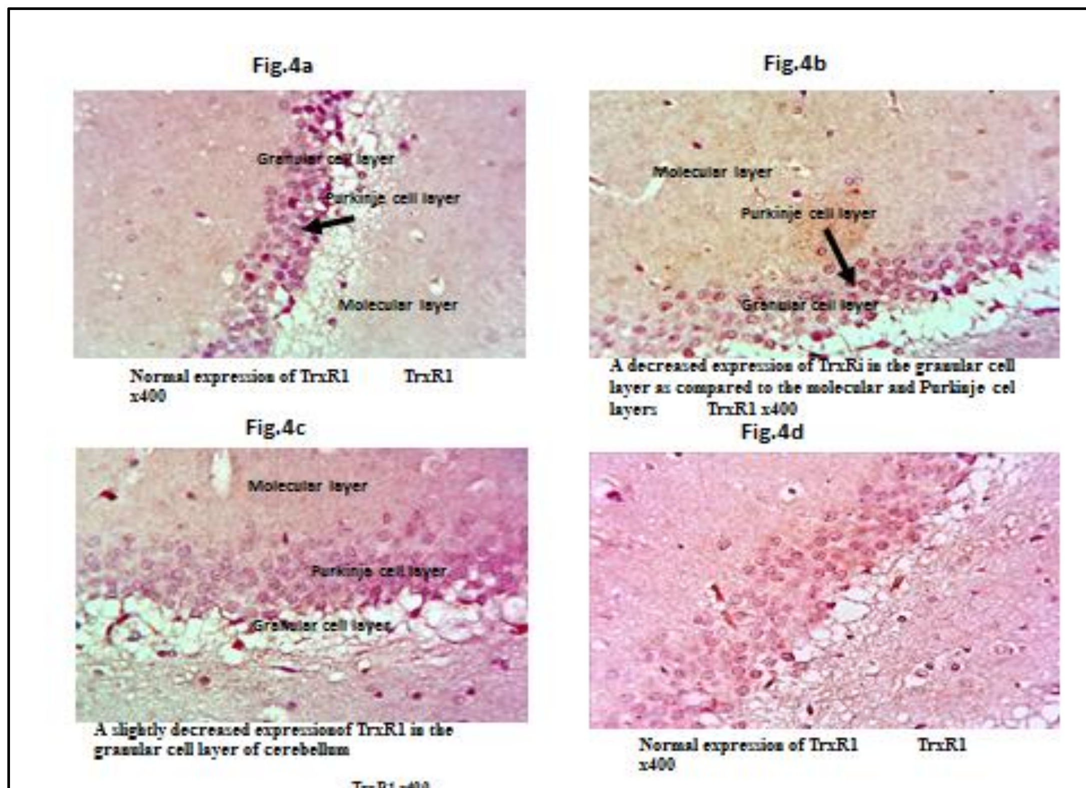

FIG.4

Fig.4a (Control) Cerebellum showing TRxR1 expression was normal. (400x). **Fig.4b** (MeHg) Cerebellum showing TRxR1 expression was decrease in granular cell layer compared with Purkinje cells and normal molecular layer (400x). **Fig.4c** (MeHg+BME) Cerebellum treated with BME showing slight decreased expression of TRxR1 in granular cell layer with almost near normal morphology (400x). **Fig.4d** (BME) Cerebellum showing normal expression of TRxR1 in Purkinje cells and molecular layer with near normal morphology (400x).

Effect of BME on Immunohistochemical changes in GFAP protein in control and experimental rats:

In control group GFAP positive (glial) cells were observed in molecular and granular cell layers (**Fig.5a**). Increased positive (glial) cells were observed inMeHg group from all layers when compared to control (**Fig.5b**). Whereas decreased GFAP positive (glial cells) were observed in BME pretreatment group (**Fig.5c**). BME alone group resembles like control having positive cells (**Fig.5d**).

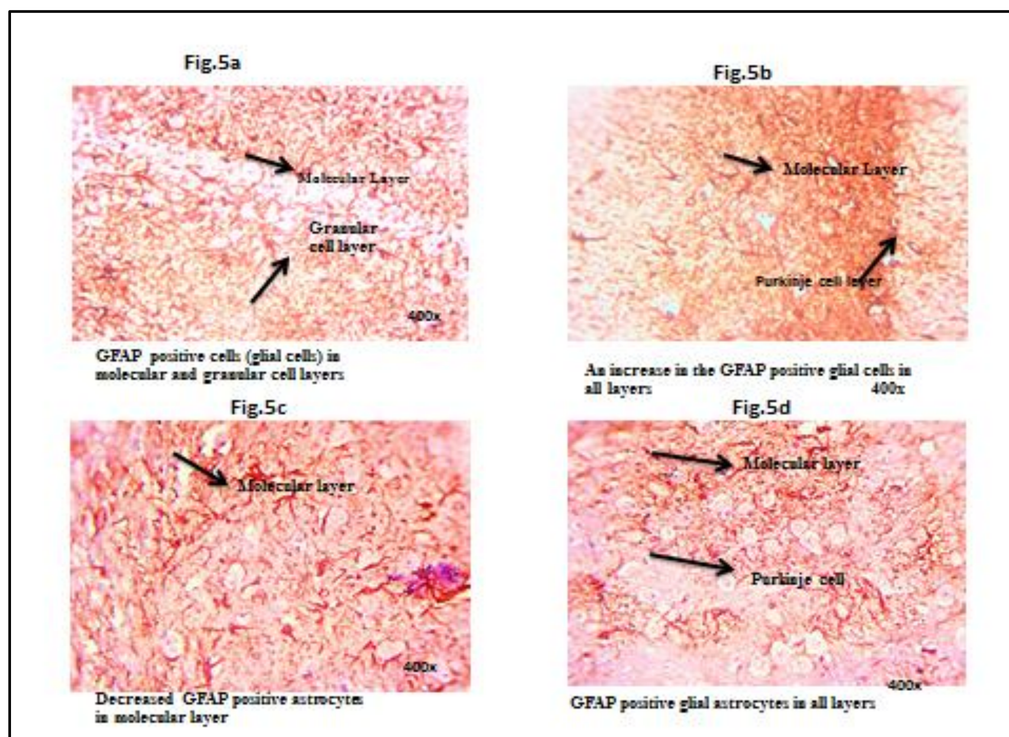

FIG.5

Fig.5a (Control) Cerebellum showing GFAP positive cells (glial cells) in molecular and granular cell layers (400x). **Fig.5b** (MeHg) Cerebellum showing an increase in the GFAP positive glial cells in all layers (400x). **Fig.5c** (MeHg+BME) Cerebellum treated with BME showing decreased GFAP positive astrocytes in molecular layer (400x). **Fig.5d** (BME) Cerebellum showing GFAP positive glial astrocytes in all layers with near normal morphology (400x).

Statistical Analysis:

Data represents mean ± S.D. Statistical comparisons were performed by one way analysis of variance (ANOVA) followed by student't' test using SPSS 10 version. If ANOVA analysis indicated significant differences, Tukey's posthoc test was performed to compare mean values between treatment groups and control. A value of $p<0.01$ was considered as statistically significant.

DISCUSSION: Oxidative stress has been known to contribute to MeHg induced central nervous system (CNS) damage. MeHg induced oxidative stress seems to be related to direct oxidative properties of MeHg toward endogenous thiol and selenol groups in low molecular weight molecules as well as proteins[29]. In our previous publications we reported have shown the beneficial effect of BME against MeHg induced neurotoxicity [24, 25, 26]

and discussed the behavioural alterations, Neurochemical changes, mitochondrial dysfunction induced by MeHg and prevented by BME.

In this current study we have studied the effects of BME on MeHg induced toxicity on towards selenoproteinslike GPx4, TRxR1 and HSP70 protein, immunohistochemical findings of GFAP and mRNA expression of Scgb3a1. We analysed the expression of GPX4 and HSP70 protein levels by western blotting. There was a significant increase in the expression of HSP70 and decrease expression of GPx4observed in MeHg intoxicated group. Glutathione peroxidase 4 (Gpx4) is a unique antioxidant enzyme that repairs oxidative damage to biomembranes. The decreased expression of GPx4 in MeHg induced group could be due to the triggering of a cellular response cascade in order to counteract the pro-oxidative outcomes induced by exposure to the organometal.

It is a versatile enzyme which is the only one out of seven isoforms in mammals able to reduce phospholipid hydroperoxides and repair oxidative damage to biomembranes[30, 31]. Hsp70 protect neurons from thermal injury, ischemia, protein aggregation, and apoptosis[32].Hsp70 has been shown to be up-regulated in the cerebellum of mice exposed to MeHg, which may represent a protective response. Our results are well in accordance with previous reports by Zemolin et al[33]. BME alters the expression of GPX4 and HSP70. *Bacopa monniera* was found to be modulating the expression of both GPx4 and HSP70 to larger extent which could be due to modulatory effect of bacosides of *Bacopamonniera*[34].

We have studied that the expression of Scgb3a1 protein level in rat cerebellum. Scgb3a1 encodes secretoglobin in 3A1 which is a secretory protein and contributes to inflammatory reactions. In our study Scgb3a1 protein levels were increased in MeHg induced group. The result obtained by this study are in agreement with Takashi et al[35], who reported that secretoglobin protein level was increased and suggesting that Scgb3a1 is a useful biomarker in indicating methylmercury exposure. Pretreatment with BME reduced the expression of this protein. These results are well in accordance with previous workreport by Viji and Helen[36], stating that BME has anti-inflammatory effect in inhibition of LOX and COX enzymes.

Immunohistochemical analyses were performed using GFAP and TRxR1 protein. Thioredoxinreductase (TrxR) enzymes are proteins that catalyze the reduction of oxidized thioredoxin by expenses of NADPH [37]. The inhibitory effects of MeHg towards correlates with the triggering of a cellular response cascade in order to counteract the pro-oxidative outcomes induced by exposure to the organometal. The selenoenzyme TRxR1 expression was found to be decreased in MeHg induced group. Our results are well in accordance with previous reports by Fujimura and Usuki[38] whom reported that methylmercury caused decreased the expression of TRxR1.

The immunohistochemical analysis showed an increase in the number of glial fibrillary acidic protein (GFAP)-positive astrocytes in MeHg induced group. GFAP is a quantitative marker of neuronal injuries on the central nervous system in vivo[39]. In accordance with Fujimura and Usuki[38], our results are also pointed out that the level of GFAP increased in MeHg toxic condition. BME pretreatment alters the immunohistochemical changes caused by MeHg.

From our results, we conclude that BME has a potential to alleviate the oxidative stress induced by MeHg. Hence, that plant can be useful in the treatment of MeHg-induced neurotoxicity.

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