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Original article

Neurobehavioral protective properties of curcumin against the mercury chloride treated mice offspring

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A B S T R A C T

In the present investigation, the effects of mercuric chloride ($HgCl_2$) on the neurobehavioural and neurochemical disruption in mice offspring was studied. A total of thirty pregnant mice were divided into six groups. Group II and III were received 150 and 300 ppm of curcumin respectively. Group IV was given 10 ppm of $HgCl_2$. Group V and VI were given 10 ppm of $HgCl_2$ with 150 and 300 ppm of curcumin respectively. In this study, treatment started from day one of pregnancy and continued until post-natal day 15 (PD 15). During weaning period, three pups in each experimental group were marked and were subjected to behavioral, physical and biochemical tests. The results revealed decreased body weight, delayed hair growth and eye opening. $HgCl_2$ treated pups taken more time in righting, rotating reflexes to return to normal placement, cliff avoidance compared to that of control group. $HgCl_2$ exposed pups showed memory and learning deficits. Anxiety behavior in treating pups was increased. Biochemical investigations showed decreased level of dopamine (DA), serotonin (5-HT) and acetylcholinesterase (AChE) in forebrain of treated pups compared to the control and curcumin groups. The protective effect of curcumin doses were significant compared to $HgCl_2$ group. The results indicated that the administration of curcumin showed effective activity towards biochemical and behavioral disorders obtained with the $HgCl_2$ treated animals. Overall, the curcumin administration revealed increased cognetion and anxiety behaviors in the treated animals. Conclusively, curcumin has a good benefits for health which can use to avoid toxicants such as Hg and other heavy metals.

1. Introduction

Mercury (Hg) occurs naturally in three forms, namely metallic Hg, organic Hg and inorganic Hg. Hg is a rare element present in the universe, but highly toxic in comparison to other heavy metals (Dash and Das, 2012). It is a nonessential metal for biological function. The main sources of Hg is from forest fires, volcanoes, movement and weathering of water (Bose-O'Reilly et al., 2010). Fossil fuels, buring of coals, manufacture of automatic machines spare parts are the important anthopogenic sources. The common forms of Hg are inorganic Hg and elemental Hg compounds (Barkay et al., 2003). The principal exposure sources of Hg, in humans, are vapor from dental amalgam, fish, seafood (organic Hg), water and air (inorganic Hg) (Omotayo et al., 2011; Oliveira et al., 2012;Ho et al., 2017). The most famous case of contamination with organic Hg is the Minamata case in the 1950/60s in Japan (Ekino et al., 2007; Franco et al., 2007; Lohren et al., 2015).

It was reported previously that almost all forms of Hg have highly toxic to the organism, causing sever damage in most of the organs and tissues. However, the toxic effect mainly depends on the chemical form, the duration of exposure, concentration of mercuric compound and the route of exposure (Clarkson, 1997; Clarkson and Magos, 2006). Chehimi et al. (2012) reported that perinatal exposure to inorganic Hg induced various alternations in mice offspring such as, decreased weight gain. Huang et al. (2008) reported that exposure to $HgCl_2$ caused neurotoxicity, including learning, memory deficit, impairment of locomotor activity, and central auditory system dysfunction.

Curcumin is a bioactive natural phytochemical compound rich in phenol found as abundant in the rhizome of turmeric plant, *Curcumincuma longa* L. It is belonging to the family Zingiberaceae (Altintas et al., 2016). Curcumin contains various health benefits and is effective to treat numerous diseases, including coryza, anorexia, cough, sinusitis and hepatic diseases (Maheshwari

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et al., 2006; Antonisamy et al., 2015). Curcumin has potential prophylactic, and therapeutic application, as antifungal, anticarcinogenic, antiviral, antimutagen, antiinfectious, antiparasitic, anti-inflammatory and antioxidant properties (Ciftci et al., 2010). Curcumin also contains neuroprotective effects and are useful to treat neurodegenerative disorders (Cole et al., 2007; Abu-Taweel GM, 2016). Many studies have revealed that curcumin exhibits various antioxidant properties (Ciftci et al., 2012; Kunihiro egt al., 2019; Tao et al., 2019; Franck et al., 2019; Chaudhary et al., 2019; Mukherjee et al., 2019; Wu et al., 2019). In general, commercially available curcumin contains approximately 3% bisdemethoxycurcumin, 17% de- methoxycurcumin and 77% curcumin (Abu-Taweel et al., 2013). This study was aimed to investigate the effects of Hg on learning and neurobehavioral changes in mice offspring. The study also aims to investigate the attenuating effects of Curcumin on behavioral and biochemical disruptions induced by $HgCl_2$ perinatal exposure.

2. Materials and methods

2.1. Animals

The Swiss-Webster strain mice (10–12 weeks old) were selected for this experiment. The male female ratio for this experiment was maintained at 1:3. All experimental animals were maintained under standard condition at Animal facility, Department of Zoology, King Saud University, Riyadh, Saudi Arabia. All procedures were performed in accordance with the ethical guidelines for the use of laboratory animals. All protocols were approved by the local Ethics and Care of Experimental Animals Committee.

2.2. Hg and administration of curcumin

The pregnant mice were divided into six groups and each group contains 10 animals. Tap water was given to the control group. Curcumin at the dose of 150 and 300 ppm was administered to group II and III. To the Group IV animals, 10 ppm of Hg Chloride was administered and Group V and VI were administrated 10 ppm of $HgCl_2$ along with 150 and 300 ppm of Curcumin. On the day of pregnancy the animals were divided into three subgroups and the experiments were carried out as described by Stiles et al. (2013).

2.3. Physical assessment during weaning period

The physical assessment such as, body weight, appearance of body hair fuzz and opening of the eyes were carried out according to the method of Abu-Taweel et al. (2012) and Ahmed et al. (2016).

2.4. Neuromotor maturation assessment

The neuromotor maturation of the developing offspring was evaluated. Righting reflex, Cliff avoidance, rotating reflex, Cliff avoidance, and rotating reflex were carried out (Abu-Taweel et al., 2014).

2.5. Behavioral assessment

2.5.1. Active avoidance responses

The active avoidance responses were evaluated in the animals as suggested by Ahmed et al. (2016) and Abu-Taweel (2018).

2.5.2. Morris water-maze test

This test is widely used to assess cognitive functions in mice models. Morris water maze test was designed as suggested previously (Morris, 1984; Rutten et al., 2002; Lamberty and Gower, 1991; Abu-Taweel et al., 2014) models.

2.5.3. Anxiety in an elevated plus - maze test

This experiment was performed as suggested previously by Wall and Messier (2001) and Walf and Frye (2007).

2.6. Biochemical studies

To carry out biochemical studies, the forebrain was isolated and frozen in liquid nitrogen for determination of neurotransmitters. The monoamine neurotransmitters dopamine (DA) and serotonin or 5-hydroxytryptamine (5-HT) were estimated as described by Patrick et al. (1991). Acetylcholinesterase (AChE) was estimated by the method of Ellman et al. (1961). Also, the non-enzymatic oxidative stress indices were determined. Lipid Peroxides was determined using a UV–visible spectrophotometer using thiobarbituric acid-reactive substances (TBARS) (Ohkawa et al., 1979). Reduced glutathione (GSH) concentration was assayed by the method of Mangino et al. (1991). Glutathione-S-Transferase, catalase and superoxide dismutase (SOD) activity were estimated (Misra and Fridovich, 1972).

2.7. Statistical analysis

All experimental data were subjected to one - way analysis of variance (ANOVA), between the experimental groups. Then, student-Newman-Keuls multiple comparison test was also performed. The levels of significance were defined at $P \leq 0.05$, $P \leq 01$, and $P \leq 001$ (Misra and Fridovich, 1972).

3. Results

3.1. Physical assessment of experimental animal during weaning period

In the present study exposure of $HgCl_2$ reduced the body weight of the offspring (Fig. 1A). The reduction was significant ($p < 0.001$) on all days of test as compared to control and Curcumin groups. The physical assessment and significant levels were described in Fig. 1B. The result was not significant significant on days 19 and 21 in low dose and on day of birth in both doses as compared to the Curcumin group. The appearance and the eys opening were delayed significantly ($p < 0.001$) in Hg exposed offspring as compared to the control and Curcumin groups. The effcts of low and high doses were statistically significant at $p < 0.01$and $p < 0.001$ level.

3.2. Neuromotor maturation during weaning period

The neuromaturation of reflexes were assessed from the first day of birth to PD21. The rotating, righting and cliff avoidance reflexes in the experimental animal which was exposed with Hg were found to be significantly suppressed. The attenuation of Curcumin doses (150 and 300 ppm) were highly significant throughout the weaning period (Fig. 2A–C respectively).

3.3. Behavioral assessment

3.3.1. Active avoidance responses

The active avoidance responses were measured in the animals, using an automatic reflex conditioner. Fig. 3A–C shows a significant decrease in number of intertrial crossings (A) ($P < 0.001$), while latency to avoid shock treatment (B) was increased significantly ($P < 0.001$). C Shows a significant decrease and ($P < 0.001$)

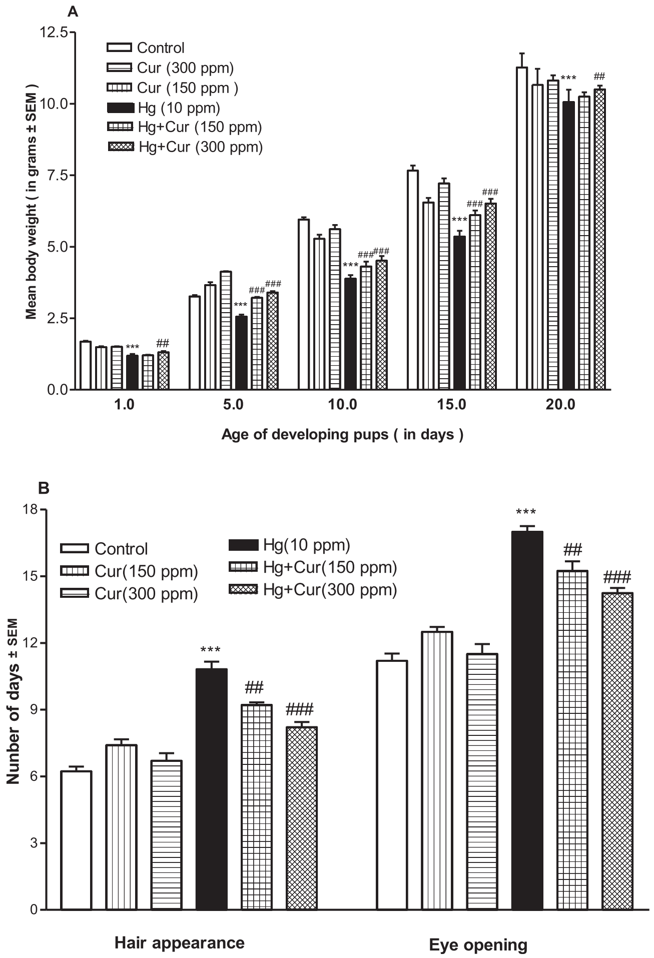

Fig. 1. A and B. Effect of perinatal Hg (10 ppm) and curcumin (150 and 300 ppm) doses, exposure on body weight gain (A) and body hair appearance and eye opening (B) in mouse pups during the weaning period. *** Statistically significant at P < 0.001 level. ## and ### represent statistically significant at P < 0.01 and P < 0.001 level.

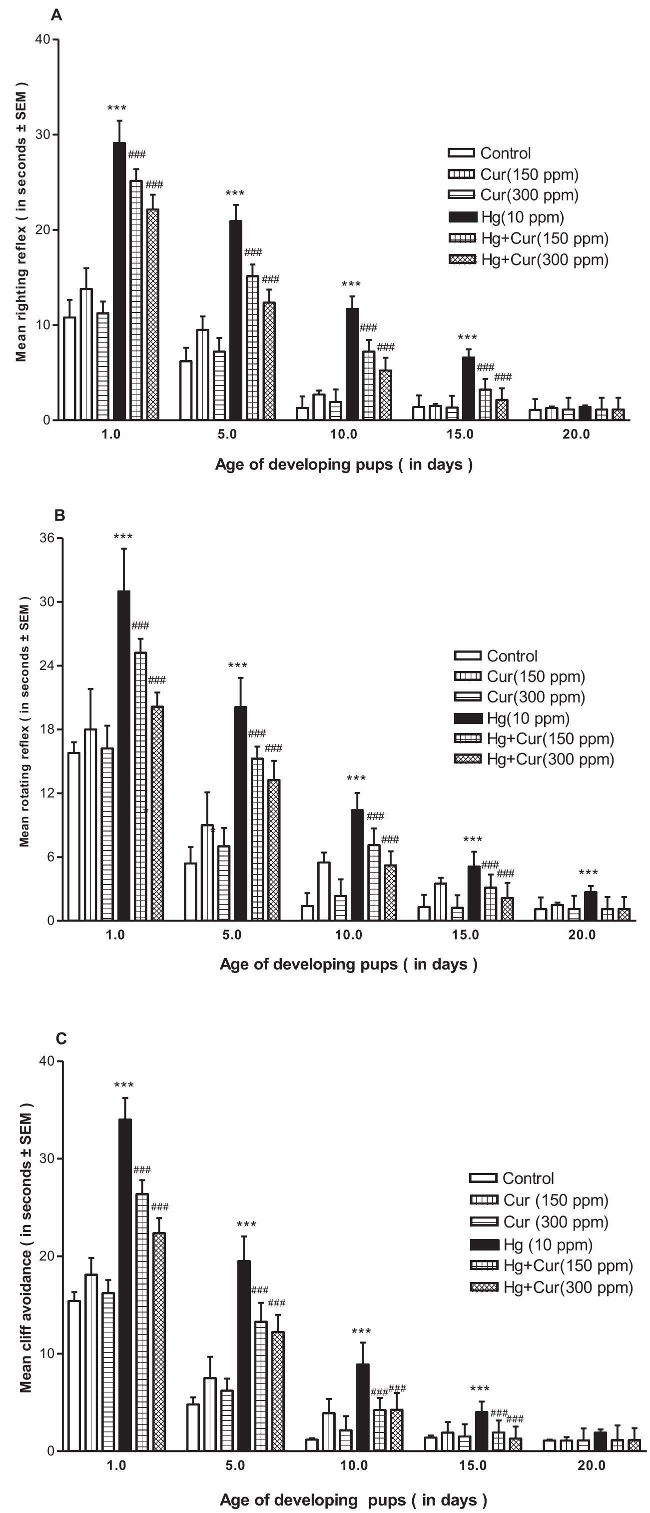

Fig. 2. A–C. Effect of perinatal Hg exposure (10 ppm) and curcumin (150 and 300 ppm) doses, exposure on righting reflex (A), rotating reflex (B) and cliff avoidance (C) of mouse pups during the weaning period. ***represent statistically significant (P < 0.001) than control and Curcumin groups; ### represent statistically significant (P < 0.001) from the Hg group.

in reinforced crossings compared to control. Low and high Curcumin doses were (P < 0.05 and P < 0.001, A; P < 0.01 and P < 0.001, B and C respectively) compared to Hg group.

3.3.2. Morris water-maze test

In this study, Hg exposed experimental mice offspring took more more time in escape latencies to reach the platform when compared with the Curcumin and control groups (p < 0.001; Fig. 4A). The number of unsuccessful trials to reach the platform was also significantly higher in Hg treated offspring as compared to the Curcumin groups and control on all testing days (p < 0.001; Fig. 4B). The probe trial revealed that Hg exposed offspring spent more time in the other three quadrants than the target (platform) quadrant as compared to the Curcumin groups and control (p < 0.001; Fig. 4C), in search of the platform. The effects of Curcumin doses were (p < 0.001) in Fig. 4A–C as copared to Hg group.

3.3.3. Anxiety in an elevated plus - maze test

Perinatal Hg exposure induced anxiety behavior changes. Fig. 5A and B showed that the treated animals were spend more time that more time (P < 0.001) into the closed arm while they were spent (P < 0.001) into open arm as compared to control and Curcumin groups (A, B) showed the number of entries into the closed arm was increased (P < 0.001) and open arm was decreased. Fig. 5A and B Indicates that the effect of Hg was ameliorated by Curcumin doses, and the p value was statistically significant (P < 0.001) as compared to Hg group.

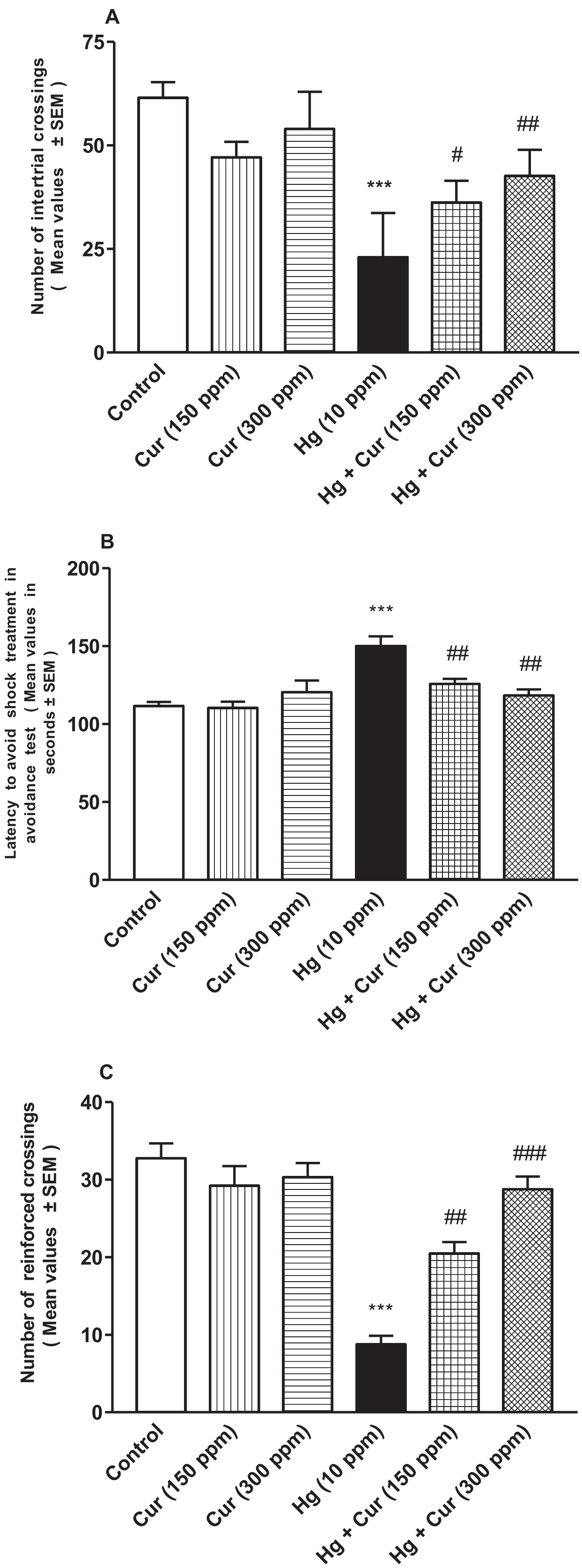

Fig. 3. A–C. Effect of perinatal Hg (10 ppm) and Curcumin exposure on the number of intertrial crossings (A), Latency to avoid shock (B) and reinforced crossings (C) of experimental animal. *** statistically significant (P < 0.001) from the control group and Curcumin groups. #, ## and ### represent statistically significant (p < 0.05, p < 0.01, p < 0.001 respectively) as compared to Hg group.

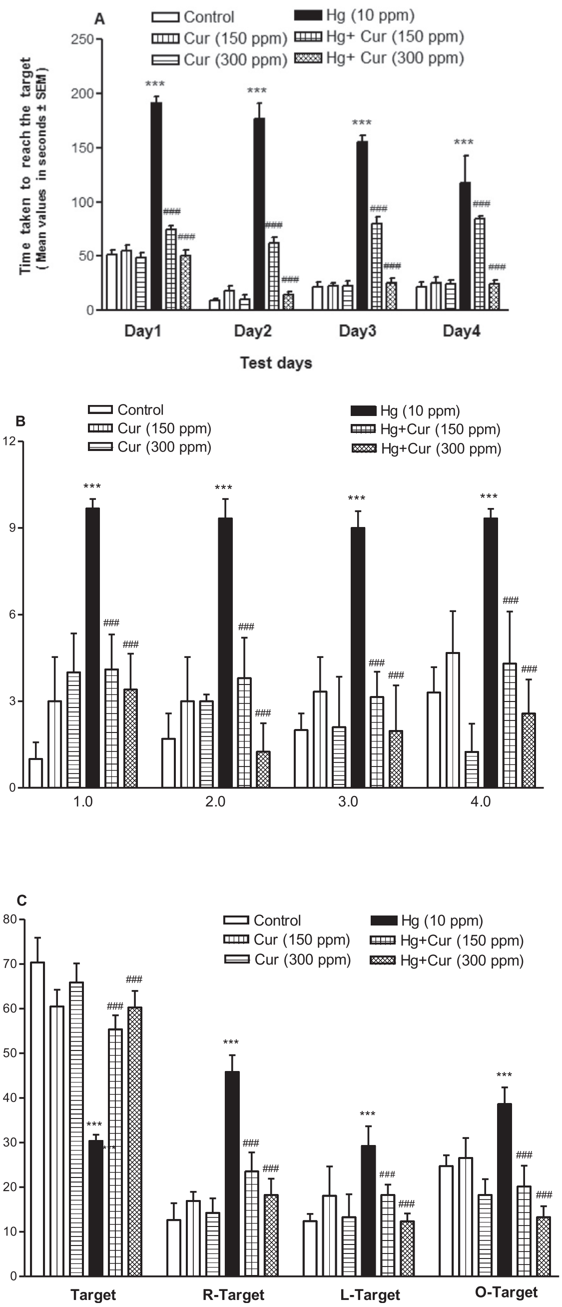

Fig. 4. A–C. Perinatal Hg exposure at 10 ppm and Curcumin application at various doses, exposure effects on the escape latencies to reach the platform (A), the number of failures (B) and the probe trial (C). *** statistically significant (P < 0.001) from the control and Curcumin groups. ### represent statistically significant (P < 0.001) from Hg group.

3.4. Biochemical studies

*3.4.1. **Monoamines and AchE level in experimental animals***

Hg exposure during lactation and gestation is highly dangerous. The level of serotonin (5-HT, B), dopamine (DA, A) and acetylcholinesterase (AchE, C) were significanlty depleted (P < 0.001) (Fig. 6A–C). However, Curcumin doses ameliorated DA, 5-HT and AchE levels was statistically significant (P < 0.001) in comparition with Hg treated group.

3.4.2. Levels of non-enzymatic oxidative stress indices

LP determined as TBARS were found to be elevated significantly (p < 0.001) due to perinatal Hg exposure in the developing

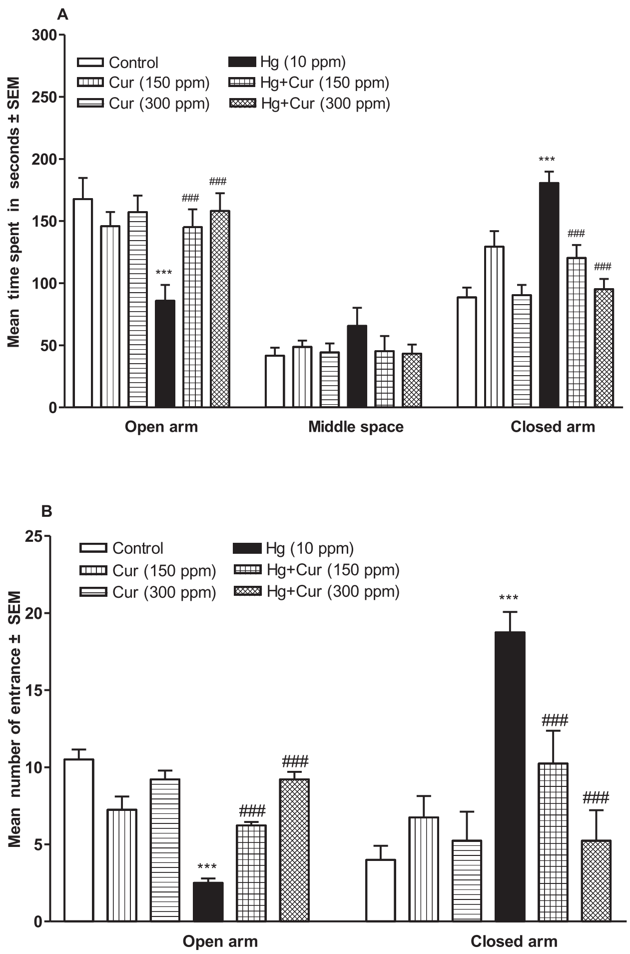

Fig. 5. A and B. Perinatal Hg exposre (10 ppm) and application of Curcumin at various doses (150 and 300 ppm); exposure effects on time spent in open and closed arms (A), the number of entries closed and open and closed arms (B). *** statistically significant (P < 0.001) from the control and Curcumin groups of animals. ### represent statistically significant (P < 0.001) from Hg exposed group.

forebrain of the offspring throughout the postnatal development period (PD 7, PD 14 and PD 21) and even at adolescent ages PD30 and PD36 (Fig. 7A). On the contrary, reduced glutathione (GSH) level remained depleted significantly (p < 0.001) at all developmental age tests as copared to the control and Curcumin groups (Fig. 7B). Fig. 7A and B showed the protective effect (p < 0.001) (p < 0.01 and p < 0.001) of Curcumin doses on TBARS and GSH in comparison with Hg group.

3.4.3. Enzymatic oxidative stress indices analysis

The enzymatic OS indices such as, GST, CAT, and SOD levels significantly depleted in experimental animal (P < 0.05, P < 0.01 and P < 0.001, respectively) which was treated with Hg in a dose-dependent manner in developing offspring (Fig. 8A–C).

4. Discussion

Mercury exists in several forms, such as elemental, metallic, inorganic, and organic. About 80% of the Hg released into the environment are metallic Hg, and mainly comes from human activities (Charlet et al., 2012; Ho et al., 2017). A few studies have reported substantial human exposure to inorganic Hg, which may come from the use of personal products, such as a skin-lightening cosmetics, traditional remedies and ritualistic and spiritual practices.

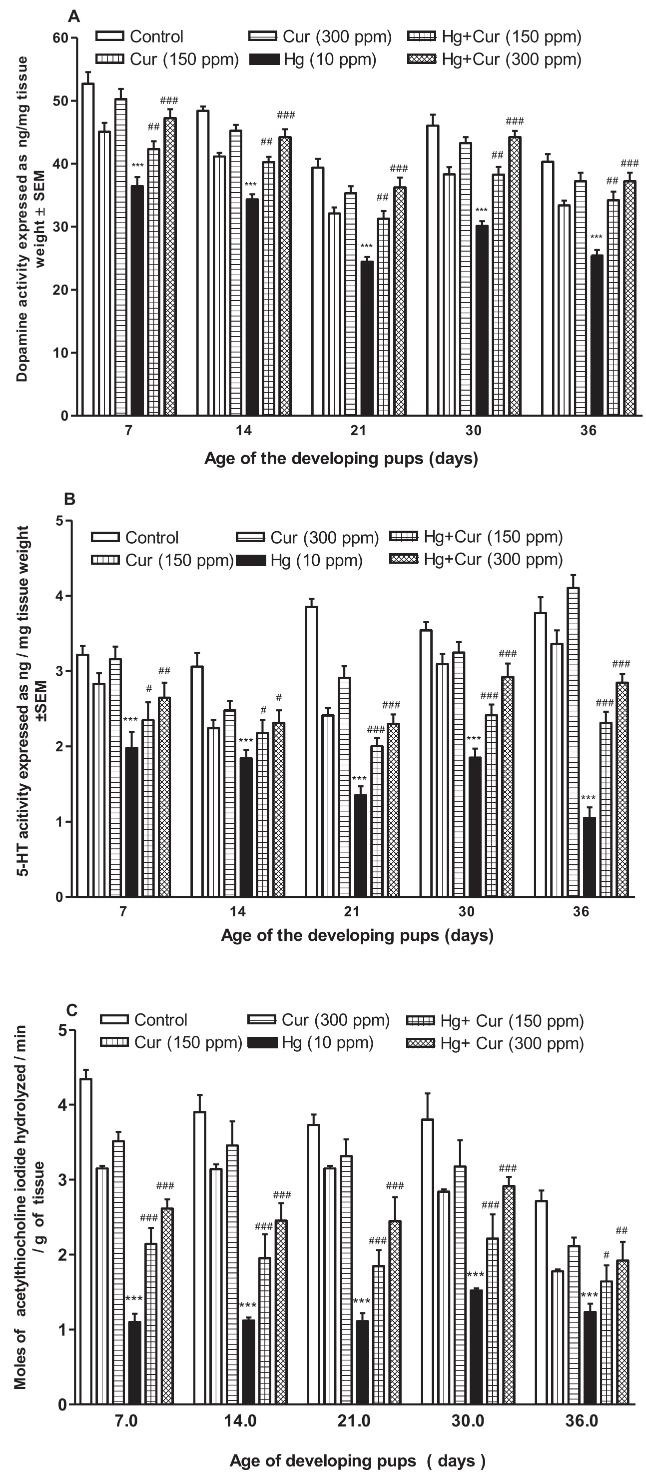

Fig. 6. A, B and C. Effect of Hg perinatal and Curcumin exposure on neurotransmitters. Hg induced a depletion in dopamine (A), serotonin (5-HT) (B) and acetylcholinesterase (AchE) (C). *** represent statistically significant (P < 0.001) from the control and Curcumin groups. #, ## and ### represent statistically significant at (P < 0.05, P < 0.01 and P < 0.001).

The toxicokinetics of Hg, including its absorption, distribution, metabolism, and excretion are highly dependent on its chemical form (Al-Saleh et al., 2016). In traditional Indian Ayuvedic medicines, Tibetan medicines and Chinese medicines, Hg sulfides have been included in the preparation of herbo-metallic substances for treatment of various diseases (Liu et al., 2016). Essential metals such as zinc, iron, cupper, magnesium, and calcium are extremely

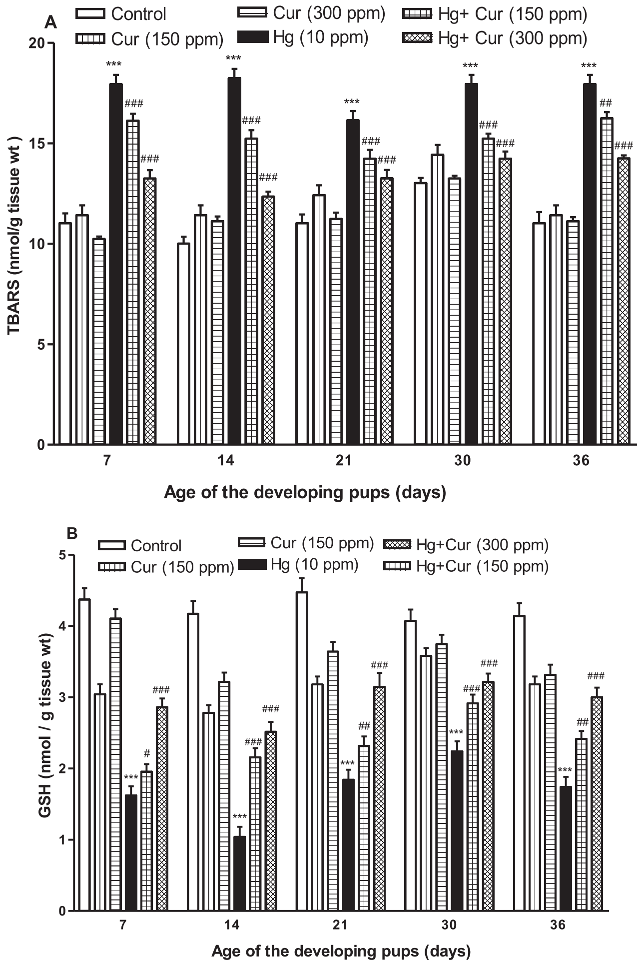

Fig. 7. A and B. Effect of perinatal Hg exposure (10 ppm) and application of Curcumin at different doses (150 and 300 ppm) on non-enzymatic oxidative stress indices; (A) lipid peroxidation content (TBARS), and (B) glutathione (GSH) level, in the forebrain of the offspring at postnatal stages. *** represent statistically significant (P < 0.001) from the control and Curcumin groups. #,## and ### represent statistically significant at P < 0.05, P < 0.001 and P < 0.001 levels.

important to mammals. Due to the extreme importance of essential metals to the newborn development as well as to a healthy adult life, the World Health Organization (WHO) highlights the necessity to maintain essential metal homeostasis (Oliveira et al., 2016). Many studies revelaed that perinatal exposure of inorganic Hg can lead to morphological and behavioral changes in humans and animal models (Chehimi et al., 2012).

This study was mainly designed to evaluate the effects of a perinatal exposure of Hg on the development of mice pups and their behaviors at adult age. The pup behavior is mainly regulated by various sensory stimulation by distal stimuli projecting from the pups or females, which elicits proximity through attention, orientation and arousal (Stern, 1990). The body weight gain of Hg chloride exposed pups was declined and dose-dependent. Our results are highly similar with previous studies (Liu et al., 2016) and disagree with Bourdineaud et al. (2012). The variation in results mainly due to differences in doses, duration, strains or nature of mercurcuminic salt (Chehimi et al., 2012). The survival of newborn rats and mice are depends on the ability of their dam to take care of them, however, the changes in maternal behavior significantly affect body weight gain in pups, because of the reduction of feeding. Maternal behaviors are regulated by dopamine (Lee et al., 2000), which altered by Hg exposure in this study. Hg exposure

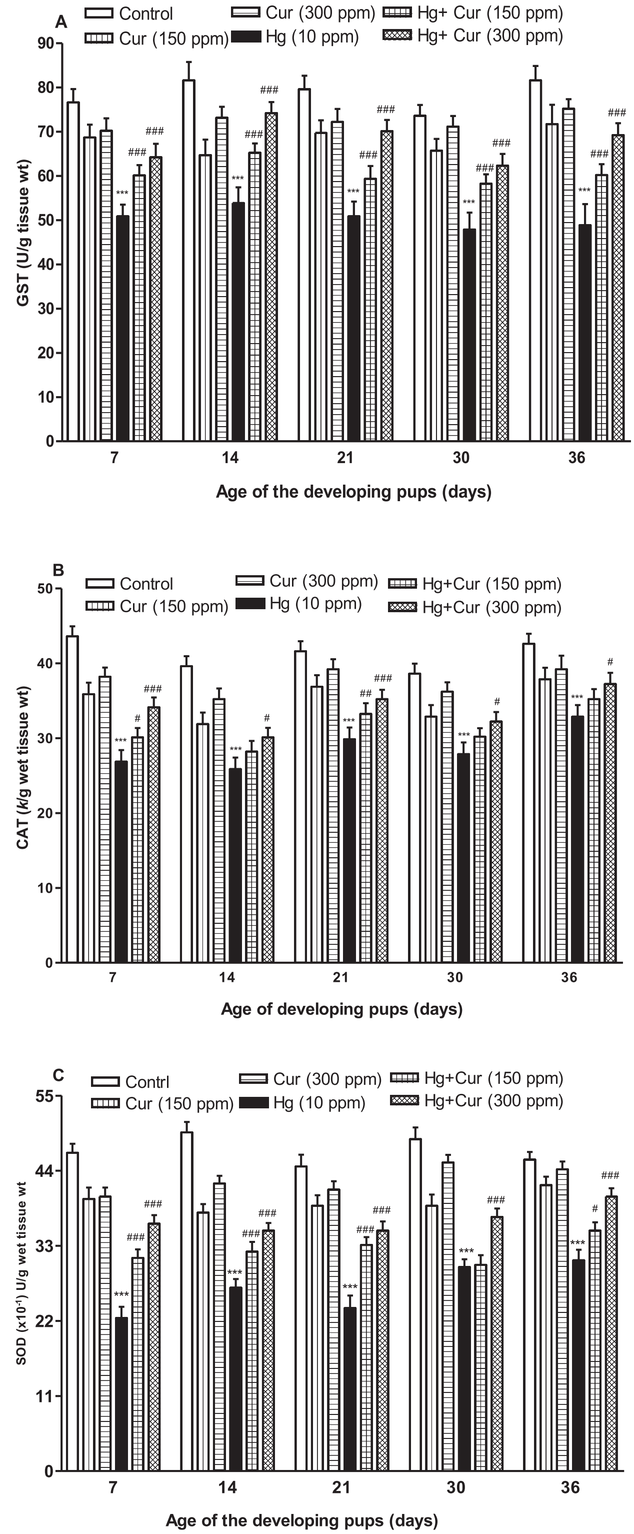

Fig. 8. A–C. Effect of perinatal Hg exposure at 10 ppm levels of enzymatic oxidative stress; (A) glutathione S-transferase (GST) activity, (B) catalase (CAT) activity, and (C) superoxide dismutase (SOD) activity in the forebrain of the offspring at various postnatal developing ages. *** statistically significant (P < 0.001) from the control and Curcumin groups. #,## and ### represent statistically significant (P < 0.05, P < 0.01 and P < 0.001 respectively) compared to Hg exposed group.

may cause alteration in the regulation of appetite also (Counter and Buchanan, 2004) or the reduction of intestinal absorption of amino acids and sugars (Chehimi et al., 2012). Previously, it was reported that the reduction of body weight gain in experimental animals exposed with Hg may be due to alteration in essential metals like Cu, Zn, Fe and Cu (Oliveira et al., 2016).

Hair appearance and the eye opening were delayed significantly in Hg exposed mice. During prenatal stage, neural tube is formed and is affected by Hg. This resulted delay in maturation of motor responses. Chehimi et al. (2012) found a delay in eye opening when pregnant animals were very much exposed to Hg chloride. The present studies showed that inorganic Hg significanlty delayed postnatal development and impaired maternal behavior. It is highly difficult to conclude that the delay in the adult age alterations and pup development are the result of a poor mothering style or direct effects of Hg prenatal intoxication (Chehimi et al., 2012). In the present study, exposure to $HgCl_2$ during lactation and pregnancy cause severe effects on the development of offspring's neuromotors. This impairment was registered in the rotating, righting, and cliff avoidance reflexes in the experimental offspring. This results are agreed with the results of Huang et al. (2011) and they disagreed with Huang et al. (2008).

Oliveira et al. (2012) reported that exposure of $HgCl_2$ cause postnatal developmental deficits and neurobehavioral changes in rodents offspring. Furthermore, in rats exposure to Hg causes long-lasting effects on learning and emotional capabilities (Chehimi et al., 2012). Hg exposure in animals and humans results in behavioral changes and intellectual impairment and it is possible that the behavioral changes could be the result of changes in the serotonin level of the brain regions (Eddins et al., 2008). In our study, the newborn mice exposed to Hg are highly anxious than that of controls. The present findings are agreed with the results of Levay et al. (2008) in experimental rats, and reported if the mothers did not deal with their offsprings properly they became more anxious. Chehimi et al. (2012) were reported high Hg levels after birth in the blood, brain and milk in mother rats.

For cognitive functions, various 5-HT receptor subtypes involve various roles in serotonergic neurotransmission, including the functions related with memory and learning processes (Spiers et al., 2001). In the present study the brain is the most susceptible organ for Hg toxicity by inhibiting the neurotransmitters DA, AchE and 5HT in the forebrain tissues. In mice the GSH develops rapidly, with significant increases in the level of GSH, GPx and glutathione reductase in the first three postnatal weeks (Stringari et al., 2008). The present study was also aimed to assess the antioxidative system in mice offspring at PD7, PD14, PD21, PD30 and PD36 stages. Perinatal Hg exposure cause enzyme imbalance and non enzymatic oxidative stress in the forebrain region in rodents (Stringari et al., 2008). It was previously suggested that the brain tissues are vulnerable to the oxidative stress (Freitas, 2009) and his stress was related to cognitive impairment in rats (Reeta et al., 2011). Thus, the cognitive dysfunction observed in the post-weaning offspring suggest for a possible strong correlation with the antioxidative defense system of the brain. Furthermore, it reflects in a way for a longer lasting effect of perinatal Hg exposure on the oxidative stress in the fore brain of the offspring.

Curcumin reportedly has potent antioxidant activities (Stajn et al., 1997), antiinflammatory (Motterlini et al., 2000) and chemoprotective properties (Ray, 2005). Curcumin in the present study had a significant ameliorating effect on the Hg-induced the development, behavioral and biochemical disorders. Furthermore, the ineffectiveness of Curcumin alone to cause any behavioral and biochemical deficits, clearly suggests that Curcumin alone is non-toxic and further supports the ameliorating effect of Curcumin on the behavioral and biochemical toxicity induced by Hg. The biochemical damage due to Hg and ameliorating effect of Curcumin in the present study may be due to the fact that Curcumin has many possible reported benefits, however; full effects are not yet fully understood and more research work is needed.

5. Conclusion

In the present study evidenced that the females treated with Hg containing drugs during pregnancy are always at a considerable risk for several complications for their fetus. To carry out a safe treatment plan during pregnancy and/or post pregnancy (lactation) period has been a formidable challenge to the clinicians since not much experimental data is available on the perinatal risks for the newborns on teratogenic effects, direct neonatal toxicity and on long-term cognitive dysfunction and oxidative stress in the brain due to perinatal Hg exposures in the newborns. The curcumin has a good benefits for health which can use to avoid toxicants such as Hg and other heavy metals. The protective effect of curcumin doses were significant compared to $HgCl_2$ group. The results indicated that the administration of curcumin showed effective activity towards biochemical and behavioral disorders obtained with the $HgCl_2$ treated animals. Overall, the curcumin administration revealed increased cognition and anxiety behavior in the treated animals. Conclusively, curcumin has a good benefits for health which can use to avoid toxicants such as Hg and other heavy metals.

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