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RESEARCH ARTICLE

Biochemical findings on cisplatin-induced oxidative neurotoxicity in rats

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Abstract

Cisplatin is an important chemotherapeutic agent used for the treatment of several cancers. However, various side effects such as neurotoxicity, nephrotoxicity, hepatotoxicity and ototoxicity restricted its usage for cancer treatment. Neurotoxicity is a clinically evident in patients that have undergone a full course of chemotherapy. Cisplatin forms DNA adducts that trigger cell death and production of reactive oxygen species inducing apoptosis. In this study, we examined our results for the first time suggesting combining cisplatin with curcumin as a combination therapy for protection and reducing side effects associated with cisplatin. Curcumin is a naturally occurring phenolic compound isolated from turmeric (*Curcuma longa*). It has antioxidant and anticarcinogenic effects. Male Wistar albino rats were allocated into four groups as follow; group I (control negative), group II (curcumin group), group III (cisplatin group), group IV (curcumin + cisplatin group). Antioxidant enzymes such as catalase and reduced glutathione were non-significantly decreased in the brain tissues of rats in cisplatin treated group and were significantly increased by pretreatment with curcumin. Also both of nitric oxide (NO) and lipid peroxidation levels were significantly increased in cisplatin treated groups and significantly decreased in groups which pretreated with curcumin.

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INTRODUCTION

Cisplatin (*cis*-diamminedichloroplatinum II) (CDDP) is one of the most potent antineoplastic agents used for the treatment of a wide variety of human malignancies such as testicular, ovarian, bladder, head and neck, cervical, esophageal as well as small cell lung cancer (Desoize and Madoulet 2002, Chen, Milacic et al. 2009, Amptoulach and Tsavaris 2011). Cisplatin treatment is plagued by severe side effects such as neurotoxicity, nephrotoxicity, ototoxicity and vomiting (Yang, Young et al. 2011, Liu, Zhang et al. 2014, Wood, Bas et al. 2014, Hinduja, Kraus et al. 2015). About 30% of patients treated with cisplatin have neurotoxicity because it can cross blood brain barrier and accumulated through repeated dosage (Namikawa, Asakura et al. 2000, Cavaletti 2008, Windebank and Grisold 2008). Only a few researches have been focused on the neurotoxicity of cisplatin (Rzeski, Pruskil et al. 2004, Nowis, Legat et al. 2007, Uğuz and Nazıroğlu 2012). Numerous studies have shown that CIS exposure disrupts the redox balance of tissues, suggesting that biochemical and physiological disturbances result from oxidative stress (Antunes, Darin et al. 2001, Silva, Antunes et al. 2001, Yamaguchi, Ishikawa et al. 2008).

The exact mechanism of cisplatin toxicity is not fully understood but it is generally accepted that cisplatin cause oxidative stress which is due to the generation of reactive oxygen species such as superoxide anion, hydrogen peroxide, hydroxyl radical which interact with DNA, lipids and proteins causing DNA damage and lipids peroxidation (Nakashima-Kamimura, Mori et al. 2009, Basu and Krishnamurthy 2010, Aydin, Unsal et al. 2011). Cisplatin can act on the sulphydryl (-SH) groups of cellular proteins (Basu and Krishnamurthy 2010), but DNA is the main target of

cisplatin that may lead to DNA damage induced by ROS and formation of platinum DNA adduct, preventing the cell division or DNA synthesis and its repair mechanism that can trigger cell death and resulting in induction of apoptosis (Sherman, Gibson et al. 1985, Eastman 1989).

Natural antioxidants have been reported to protect against cisplatin toxicity. Several studies have been reported that supplementation with antioxidants prevent neurotoxicity associated with platinum based chemotherapy which work together to enhance the anticancer activity and reduce adverse effects (Pace, Giannarelli et al. 2010, Mendonca, da Silva Machado et al. 2013, Turan, Cayir et al. 2014). Curcumin is a dietary antioxidant derived from turmeric (*Curcuma longa*) (Araujo and Leon 2001, González-Salazar, Molina-Jijón et al. 2011). It exhibits its antioxidant activity by preventing lipid peroxidation, regulates cellular antioxidant enzyme such as catalase, superoxide dismutase and glutathione peroxidase (Soobrattee, Neergheen et al. 2005, Barzegar and Moosavi-Movahedi 2011) and inhibits the expression of iNOS (Camacho-Barquero, Villegas et al. 2007).

Numerous studies have reported that the neuroprotective activity of curcumin is due to its ability to cross blood brain barrier (Yang, Lim et al. 2005, Garcia-Alloza, Borrelli et al. 2007).

Based on this information, the main purpose of this study is to evaluate the neuroprotective effect of curcumin on cisplatin induced neurotoxicity by evaluating some antioxidant and lipid peroxidation status of brain of rats to assess cisplatin induced neurotoxicity in the present investigation.

1. Materials and methods

2.1. Chemicals

Curcumin and corn oil were purchased from Sigma chemical Company (Sigma, St. Louis, Mo, USA). Cisplatin was purchased from Mylan. S.A.S. (Saint-Priest-France). Commercial assay kits for catalase, glutathione, malondialdehyde were purchased from Bio-diagnostic Company (29 Tahreer St., Dokki, Giza, Egypt). All other reagents were of analytical grade and the purest quality available

2.2. Animals and experimental design

Forty healthy and adult male Wistar albino rats (80-120 g) were obtained from the animal house of the faculty of pharmacy, Beni-Suef University. The animals were kept under standard laboratory conditions (12 h light/dark cycles, 26-28 °C). They were fed with standard laboratory diet and given water ad libitum. The rats were maintained under standard conditions in the animal house as per the guidelines of Beni-Suef University Committee for the Purpose of Control and Supervision on Experiments on Animals. After one week of adaptation, rats were randomly divided into 4 groups (10 rats each). Group I (control negative group). Rats in group II (curcumin group) were orally administered with curcumin at the dose of 200 mg/kg /day (Bayrak, Uz et al. 2008) for 10 consecutive days. Rats in group III (cisplatin group) were injected intraperitoneally with cisplatin at a single dose of 7 mg/kg (Saleh and El-Demerdash 2005, Saleh, Ain-Shoka et al. 2009, Arjumand and Sultana 2011). Rats in group IV (curcumin+ cisplatin group) were injected intraperitoneally with cisplatin at a single dose of 7 mg/kg after 10 days of orally pretreatment with curcumin at the previous doses as in group II. Then, animals were sacrificed, and samples of brain tissues from each group were collected for biochemical examination.

2.3. Sampling

Rats were sacrificed for brain tissue collection. Brain tissue sample, 0.5 g was homogenized in ten volumes of ice cold phosphate buffer (pH 7) until a uniform suspension was obtained. The homogenate was centrifuged at 20000×g for 10 min at 4 °C. The supernatant was collected and stored at -20 °C for biochemical determination of MDA, NO, GSH and catalase.

2.4. Biochemical analysis

Antioxidant parameters including reduced glutathione (GSH) and catalase activity were measured in brain tissue homogenate using commercially available kits (Biodiagnostic, Cairo, Egypt), according to (Beutler, Duron et al. 1963, Aebi 1984) respectively. Also lipid peroxidation (malondialdehyde (MDA) was measured according to (Ohkawa, Ohishi et al. 1979) by using of the commercially available kits (Biodiagnostic, Cairo, Egypt). Quantitative determination of total nitric oxide (NO) in brain homogenate was measured by using of ELISA kit (Catalog number 917-020) which purchased from (Assay designs, U.S.A) (Bellos, Perrea et al. 2011).

2.5. Statistical analysis

Statistical analysis was carried out using Graph Pad Prism software (version 6). The significances of differences among testing groups were analyzed using one way ANOVA followed by Turkey's post hoc test. Values of $P < 0.05$ were regarded as significant. The data, as clearly indicated are reported in tables as mean \pm standard deviation (S.D).

3. Results

3.1. Effect of curcumin pretreatment on some antioxidant parameters and lipid peroxidation of brain tissue homogenates of rats injected with cisplatin.

Intraperitoneal injection of a single dose of cisplatin (7 mg/kg B.W.) caused a non- significant ($p < 0.05$) decrease in the catalase level in brain tissue homogenates in group IV in comparison with the group I as shown in table (1). Pretreatment with curcumin showed a significant ($p < 0.05$) increased in the level of catalase in brain tissues homogenates when compared with group I (control negative) and group III (cisplatin group). Administration of curcumin alone (group II) resulted in a significant increase in the level of catalase in brain tissue homogenates of rats in comparison with group I (control negative group).

As shown in table (1) administration of cisplatin to rats (group III) resulted in non-significant decreased the glutathione content when compared to the group I. Pretreatment with curcumin (group IV) ameliorated the side effect of cisplatin and the level of reduced glutathione of brain tissue homogenates were significantly ($p < 0.05$) increased when compared to group III (cisplatin group). Administration of curcumin alone (group II) exhibited no significant effects in GSH level in brain when compared to the control group (group I).

Malondialdehyde (MDA) level is considered a biomarker of lipid peroxidation. Results in table (1) revealed that the MDA level of brain homogenates of rats in group III was significantly ($p < 0.05$) increased in comparison to group I. Pretreatment with either curcumin (group IV) significantly decreased lipid peroxidation induced by cisplatin injection, while treatment with curcumin alone showed no significant alteration in MDA level. These results clearly indicated the protective antioxidant effects of curcumin against cisplatin induced lipid peroxidation in brain tissue of rats.

The results about NO level of brain tissue of rats were the same as that reported for MDA in table (1).

Table.1 Effect of curcumin pretreatment on cisplatin induced oxidative stress in brain tissue homogenates of rats:

| groups | Group I | Group II | Group III | Group IV |
|-----------------------|-------------------------|-------------------------|-------------------------|----------------------------|
| Catalase (U/g tissue) | 89.00±1.00 | 97.35±4.00 | 73.25±1.49 | 190.77±12.52 ^{ab} |
| GSH (nmol/g.tissue) | 0.23±0.01 | 0.25±0.009 | 0.15± 0.006 | 0.58 ± 0.06 ^{ab} |
| MDA(nmol/g.tissue) | 14.28±2.85 ^b | 19.27±3.01 ^b | 61.16±8.20 ^a | 39.9±2.1 ^{ab} |
| NO (nmol/mg) | 1.45±0.19 ^b | 1.53±0.20 ^b | 13.02±1.14 ^a | 5.45±0.46 ^{ab} |

Values are expressed as mean ± SEM for ten animals in each group.

a $P < 0.05$, a significant difference in comparison with the control group

b $p < 0.05$, a significant difference in comparison with cisplatin group

Group I (control negative group), Group II: CMN treated group (200 mg/kg B.wt/day for 10 consecutive days), Group III: CDDP (7 mg/kg B.wt.), Group IV: CMN (200 mg/kg B.wt. for 10 consecutive days) + CDDP (7 mg/kg B.wt I.P as a single dose).

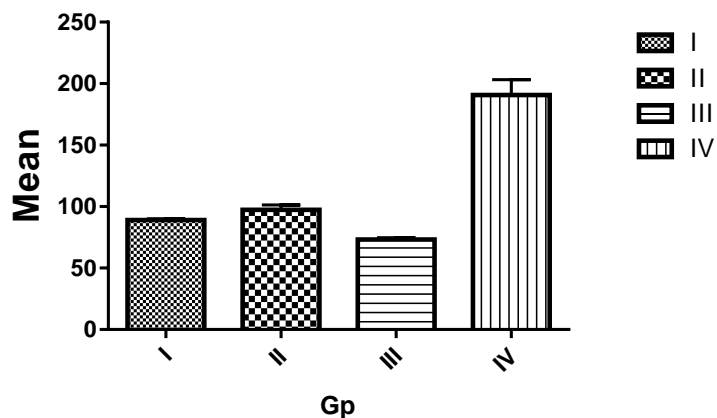


Figure (1): The mean value of catalase level in the brain tissue in groups treated with curcumin compared to cisplatin treated group.

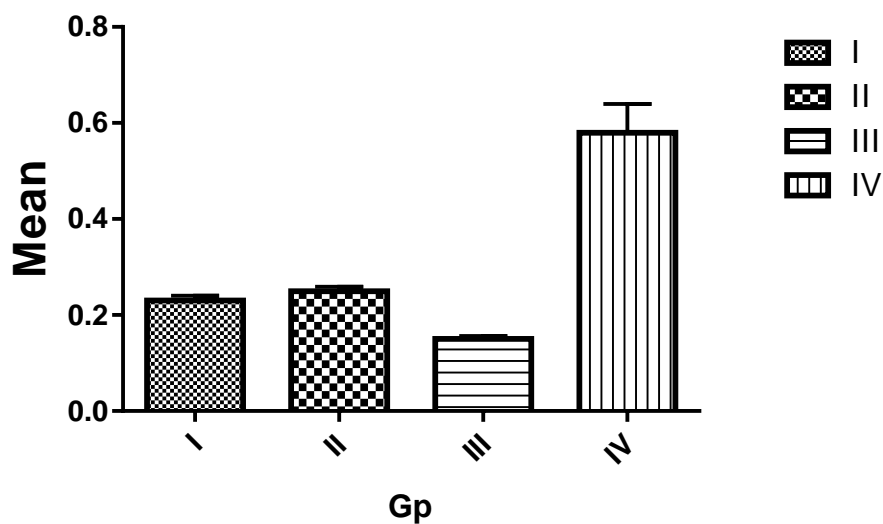


Figure (2): The mean value of glutathione level in the brain tissue in group treated with curcumin compared to cisplatin treated group.

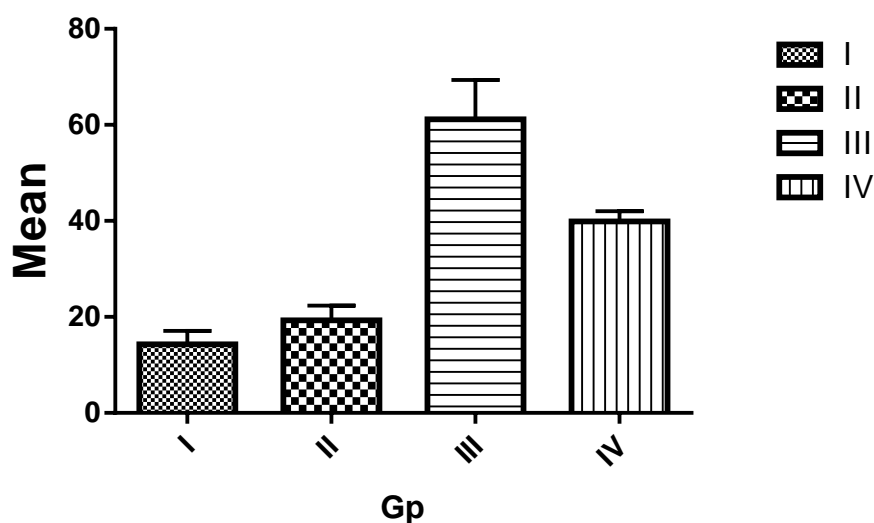


Figure (3): The mean value of MDA level in the brain tissue in groups treated with curcumin compared to cisplatin treated group.

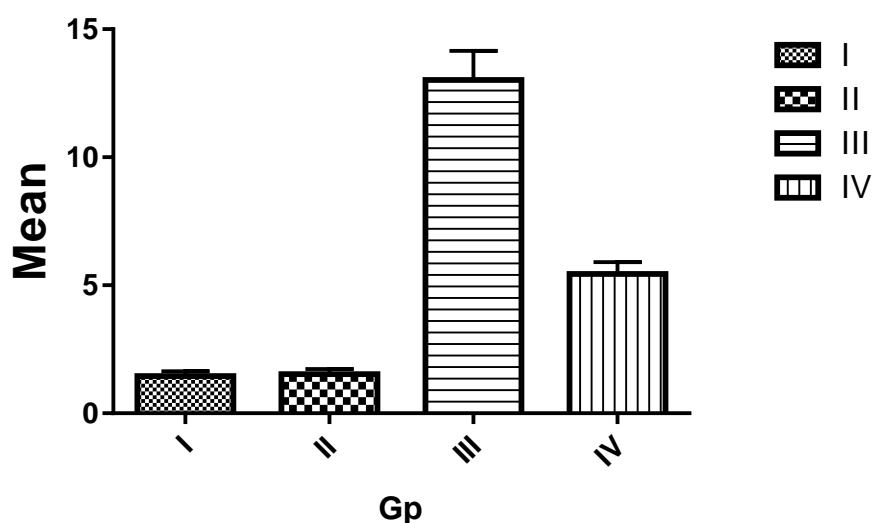


Figure (4): The mean value of nitrite level in the brain tissue in groups treated with curcumin compared to cisplatin treated group.

4. Discussion

Most chemotherapeutic agents for cancer treatments are associated with serious side effects and systemic toxicity including neurotoxicity, nephrotoxicity and hepatotoxicity (Kim, Jeong et al. 2010, Maggioni, Nicolini et al. 2010, El-Awady, Moustafa et al. 2011, Galluzzi, Senovilla et al. 2012). Neurotoxicity is the major dose limiting side effect of cisplatin toxicity (Turan, Cayir et al. 2014).

Cisplatin increases the production of free oxygen radicals and decreases the antioxidants, thus resulting in the disturbance of the oxidant/ antioxidant balance (Kawai, Nakao et al. 2006, Lawenda, Kelly et al. 2008). Reactive oxygen radicals accumulated in tissues resulted in production of hydroxyl radicals, superoxide anions, nitric oxide and hydrogen peroxide (Kart, Cigremis et al. 2010). Thus ROS affect the antioxidant defense mechanism, reduce the intracellular concentration of GSH, decrease the activity of GSH and enhances lipid peroxidation process leading to elevation of MDA levels (Manna, Sinha et al. 2006) and reduce Catalase level (Rybak, Husain et al. 2000). Oxidative stress is defined as an imbalance between the production and removal of ROS. This may be originated by an over production of oxidant or by the depletion of antioxidant compounds (Halliwell 2006).

Catalase (CAT) is an enzymatic antioxidant which catalyzes the degradation of hydrogen peroxide (H₂O₂) and other peroxides such as lipid peroxides in cell membrane into oxygen and water, using glutathione as a substrate (Srividhya, Jyothilakshmi et al. 2008). The current study demonstrated (table 1) that the level of catalase in the brain tissues markedly decreased in cisplatin treated group compared to the control. This data was coincided with previous studies of (Hassan, Chibber et al. 2013, Kamisli, Ciftci et al. 2014), who reported that cisplatin induced neurotoxicity characterized by a significant reduction in the catalase and GSH activity in rats brain tissues. Additionally, (Sahin, Tuzcu et al. 2010, Ahmed, Omar et al. 2011, Khan, Khan et al. 2012), found that the activity of antioxidant enzymes such as catalase was significantly decreased in kidney, testicular tissues and jejunum respectively in the cisplatin injected rats in comparison with the normal control rats.

Glutathione (GSH) is one of the most important naturally occurring non-enzymatic antioxidant, which prevent the damage of cellular components caused by reactive oxygen species or oxidative stress (Choi, Cho et al. 2003). GSH is well known for its antioxidant activity in the CNS. In fact, GSH is so important to redox homeostasis in many cells. GSH is a potent scavenger for free radical species superoxide anion, nitric oxide, hydrogen peroxide radicals and peroxynitrite (Aoyama, Watabe et al. 2008). MDA is the major end products of peroxidation of unsaturated fatty acids which is responsible for cell membrane damage and is considered a good marker for ROS in lipid peroxidation during oxidative stress (Pan, Mukhopadhyay et al. 2009). Our investigation as reported in table (1) observed that the MDA level was significantly increased and GSH activity was non-significantly decreased in the brain tissues of cisplatin treated group compared to the control one. This might be due to reduction of bioavailability of GSH during enhancement of lipid peroxidation process resulting from oxidative stress caused by cisplatin. This data was in agreement with (Hassan, Chibber et al. 2013, Waseem and Parvez 2013, Akman, Akman et al. 2015), who reported that cisplatin result in a significant increase in lipid peroxidation in the brain tissues and the ear as a result of cisplatin induced neurotoxicity.

Nitric oxide (NO) is defined as a short lived free radical which is synthesized under oxidative stress by inducible nitric oxide (iNOS) (MacMicking, Xie et al. 1997). which its expression regulated via nuclear translocation of the transcription factor Kappa NF- κ B (Epstein, Barnes et al. 1997, Bogdan 1998). Under simultaneous generation of ROS and NO in combination together as a result of oxidative stress NO can interact with ROS forming peroxynitrite which is a powerful cytotoxic agent cause induction apoptosis, inhibition of cellular antioxidant activity, induction of LPO and decreasing glutathione level (Zhang, Walker et al. 2000, de Pinto, Tommasi et al. 2002, Zaninotto, La Camera et al. 2006). The present study demonstrated that the level of NO of brain tissue in the cisplatin treated group significantly increased compared to the control negative group as shown in table (1). This data was in agreement with previous studies of (Hassan, Chibber et al. 2013) that reported a significant increase in NO level after cisplatin treated rats compared to normal control animals.

This might be as a result of ROS and RNS production which affect the expression iNOS via activation of proinflammatory cytokines.

Curcumin is a lipophilic non flavonoid naturally occurring antioxidant. It is a potent free radical scavenger for reactive oxygen species as it inhibits lipid peroxidation and enhances catalase activity (Vajragupta, Boonchoong et al. 2003, Al-Omar, Nagi et al. 2006, Yang, Zhang et al. 2009). Results in table (1) showed that pretreatment with curcumin resulted in a significantly increased in the catalase activity in brain tissues of rats (group IV) when compared to (group III). Our data was in harmony with (Subudhi and Chainy 2010), who reported that curcumin caused a significant elevation in catalase level in the liver in L-thyroxine-induced hyperthyroid in rats. Also reported in table (1), that pretreatment with curcumin was significantly increased the GSH level of brain of rats (group IV) and significantly decreased the level of MDA of the same group in comparison with (group III). This was coincided with a previous study of (Waseem and Parvez 2013), who reported that curcumin pretreatment developed more antioxidant effect in brain by significant restoration the GSH level and suppression the elevated MDA level. This might be due to the neuroprotective effects of curcumin which is act as a powerful ROS scavenger (Kluth, Banning et al. 2007, Barzegar and Moosavi-Movahedi 2011) and reduced the oxidative stress marker of lipid peroxidation (Singh and Singh 2011).

Additionally, this results was in agreement with (Ilbey, Ozbek et al. 2009), who mentioned that curcumin treatment significantly decreased the highly level of MDA and increase the GSH activity in rat testis treated with cisplatin. Also our results reported that pretreatment of rats with curcumin (group IV) significantly decreased the NO level compared to the cisplatin treated rats (group III). This results indicated that curcumin can counteract the effect of cisplatin as a powerful neurotoxin also can scavenge the ROS through its antioxidant, antiinflammatory activity and its reduction of nuclear transcription factor NF- κ B (Singh and Aggarwal 1995) and iNOS activity. This was in agreement with (Ilbey, Ozbek et al. 2009), who mentioned that curcumin treatment significantly decreased the elevated of iNOS and NF- κ B expression in the testicular tissue of cisplatin treated rats resulting in decreasing NO and ROS thus, inhibiting the cytotoxic effect of cisplatin.

In conclusion, results of the current study evaluated that oxidative stress and nitrosative stress along with lipid peroxidation are important features in cisplatin neurotoxicity. Based on the observation of this study the pretreatment with curcumin may be beneficial in preventing the cisplatin induced neurotoxicity.

5. Conclusion

The concept of the present study was to investigate the possible neuroprotective effects of natural antioxidants such as curcumin, a polyphenolic non-enzymatic antioxidant against cisplatin induced neurotoxicity. We have observed that the pretreatment with curcumin showed a markedly protection against cisplatin induced oxidative neurotoxicity.

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