Hepatoprotective Effect of Andrographis paniculata against Oxidative Damage Caused by Cisplatin in Rats

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Abstract

The role of ethanolic extract of Andrographis paniculata (AP), in preventing cisplatin (CP) induced oxidative damage in rat liver was studied. The study included 60 Wistar albino rats were divided into 12 rats in each group. Group I served as normal control group. To group II rats, CP was administered at 7.5mg/kg body weight intraperitoneally for single dose. Rats in group III were administered AP at the dose of 500mg/kg body weight for 45 days. Group IV rats were pre-treated with AP 15 days prior to CP administration and followed by AP treatment for 45 days. Rats in group V were administered with CP and concurrently treated with AP extract at 500mg/kg by oral gavaging for 45 days. The liver samples collected at 7th, 14th, 28th, and 45th day of the study were subjected for estimation of endogenous antioxidant enzymes (SOD, CAT and GPx) and malondialdehyde (MDA). Significant decrease (P<0.05) in the levels of antioxidant enzymes and increase in MDA levels were recorded in CP treatment group. The AP treatment groups revealed a significant recovery (P<0.05) all enzymes and decrease in MDA levels which suggested that AP has a good antioxidant effect and could be effectively used for prevention of toxic side effects of CP.

Keywords
Cisplatin, antioxidants, hepatotoxicity, Andrographis paniculata, Malondialdehyde

Introduction
Cisplatin is a platinum-based alkylating antineoplastic agent and used as the backbone of myriad treatment regimens across a broad spectrum of malignancies (Crona et al., 2017). Among the anti-tumor drugs, cisplatin occupies a very important place, as its therapeutic efficacy for certain cancer types is remarkably high. Cisplatin-based blended chemotherapy regimens are presently used as a significant therapy in the treatment of
testicular cancer, ovarian germ cell tumors, epithelial ovarian cancer, head and neck cancer, advanced cervical cancer, bladder cancer, mesothelioma, endometrial cancer, non-small cell lung cancer, malignant melanoma, carcinoids, penile cancer, adrenocortical carcinoma etc. in humans (Hill and Speer, 1982 and Galanski, 2006).

The toxic effects of cisplatin are due to its close interaction with DNA molecules. Cisplatin thus arrests DNA synthesis and replication in rapidly proliferating cells (Rastogi et al., 2014). Cisplatin does not distinguish between a malignant and normal fast-growing cell, hence, eliminates both type of cells by exerting several toxicities as its side effects such as nephrotoxicity, hepatotoxicity, cardiotoxicity, gastrotoxicity, ototoxicity, neurotoxicity, myelosuppression and thrombocytopenia (Dasari and Tchounwou, 2014).

Hepatotoxicity is one of the major side effects of cisplatin produced at high doses (Kim et al., 2004). The exact mechanism of cisplatin induced hepatotoxicity is not known, however oxidative stress induced by cisplatin might be one of the causes. Along with interaction with DNA, the oxidative stress that occurs during biotransformation of the drug is also one of the most important mechanisms involved in cisplatin-induced toxicity resulting in the enhanced production of reactive oxygen species, reduction in the mitochondrial membrane potential and decrease in antioxidant enzymes (Saad et al., 2004).

Cisplatin induces oxidative stress in liver by enhancing the production of reactive oxygen species (ROS), like superoxide, hydrogen peroxide, hydroxyl ions and oxygen free radicals and nitrogen reactive species (NRS). The imbalance between formation of ROS and RNS in metabolism leads to pathological consequences in the liver (Yilmaz et al., 2005). Since long time, alleviation of cisplatin induced toxicity has been the prime concern during therapeutic intervention with cisplatin.

There is an increasing interest in the use of phytochemicals, medicinal plants and their formulations for evaluating their efficacy in combination with chemotherapeutic agents in traditional system of medicine and in ethnomedical practices to prevent toxic effects of chemotherapeutic agents (Singh and Aggarwal, 2006). Many antioxidants, herbal plants and phytochemical compounds have been studied as protective agents to scavenge free radicals formed by exposure to cisplatin (Abdelmeguid et al., 2010).

Andrographis paniculata is one such important medicinal plant widely used around the world. It belongs to the family Acanthaceae and most commonly used in the traditional systems of Unani and Ayurvedic medicines and is considered as “king of bitters”. It is an annual plant, It grows in hedge rows throughout the plains of India and is also cultivated in gardens (Hossain et al., 2014).

Phytochemical analyses of Andrographis paniculata have revealed that it is a rich source of diterpenoids, andrographolide, neo-andrographolide, 14-deoxyandrographolide, iso-andrographolide, 14-β-deoxyandrographolide, 19-β-glucoside, homo-andrographolide, andrographan, andrographosterin, and stigmasterol.

Andrographolide is the primary bioactive phytochemical of Andrographis paniculata and it exhibits significant anti-oxidant, anti-inflammatory and has chemo-protective potential towards normal cells (Bardi et al., 2014). The present study aimed to investigate the possible protective effect of Andrographis paniculata on antioxidant enzymes and lipid peroxidation.
Materials and Methods

Drugs and chemicals

Cisplatin (Kemoplatis) was procured from Fresenius Kabi India Pvt. Ltd. Pune, India, and the ethanolic extract of Andrographis paniculata was obtained from Himalaya Herbal Pvt Ltd. Bangalore, India.

Animals

Normal adult Wistar albino rats weighing approximately 180-200 grams were procured from commercial animal facility, Bangalore for the study. They were maintained under standard laboratory conditions and fed with ad libitum standard commercial rat feed and clean drinking water. The duration of experiment was for a period of 45 days and a prior permission was obtained from the Institutional Animal Ethics Committee (IAEC) for the conduct of the experiment.

Experimental design

The rats were maintained under standard laboratory conditions for a period of 15 days for acclimatization in the experimental animal house. The rats were divided, based on the body weight, into five groups with twelve rats in each group. Group I was kept as normal control and injected with 0.5ml sterile PBS intraperitoneally on Day 1 and gavaged with PBS daily. Group II was positive control and hepatotoxicity induced with administration of cisplatin at 7.5mg/kg body weight for single dose.

Group III was supplemented with ethanolic extract of Andrographis paniculata alone at the dose rate of 500 mg/kg body weight. Group IV was supplemented with Andrographis paniculata extract at the dose rate of 500mg/kg body weight concurrently with administration of CP.

Collection of liver samples

To study the progressive effects of the treatments given to different groups, rats from each group were sacrificed humanely under ketamine hydrochloride on 7th, 14th, 28th, and 45th day of the experiment. Liver from all the group of animals were collected in chilled normal saline and then transferred to -80°C for further analysis.

Estimation of superoxide dismutase (SOD)

Superoxide dismutase activity was determined by the method described by Marklund and Marklund(1974). The enzyme activity was expressed in terms of units per minute per mg of protein. One unit of SOD was defined as the amount of enzyme required to inhibit pyrogallol auto-oxidation reaction by 50 percent.

Estimation of catalase (CAT)

Catalase was estimated by the method described by Caliborne (1985). Enzyme activity was expressed as µmol of H₂O₂ decomposed per minute per mg of protein.

Estimation of glutathione peroxidase (GPx)

Glutathione peroxidase was determined by themethod described by Rotruck et al., (1973). Enzyme activity was expressed as units per mg protein.

Estimation of TBARS (Malondialdehyde):

Lipid peroxidation in the liver tissue was determined by estimation of thiobarbituric acid reactive substance (TBARS) by the
method of Yagi (1976). The unit of activity was expressed as n moles of MDA /mg of tissue.

Results and Discussion

The effect of CP administration on the antioxidant enzyme status and lipid peroxidation in liver of rats was analyzed. The results indicated that CP caused a significant decrease [P<0.05] in the levels of SOD, CAT and GPx (Tables 1,2,3 and Figure 1,2,3) and significant increase [P<0.05] in the level of MDA (Table 4 and Figure 4) in Group- II when compared to other groups, throughout the duration of the experiment.

These findings indicated that cisplatin treatment can induce liver damage through oxidative stress. Under normal physiological conditions, cells control reactive oxygen species levels by balancing the generation of reactive oxygen species with their elimination by scavenging system. But under oxidative stress conditions, excessive reactive oxygen species generated can damage cellular proteins, lipids and DNA, leading to fatal lesions in cells.

Oxidative stress is one important mechanism involved in the cisplatin hepatotoxicity. The mitochondria are the primary target in cisplatin toxicity with loss of mitochondrial protein sulfhydryl group and reduction in the mitochondrial membrane potential (Saad et al., 2004). Mitochondrial glutathione (GSH) is essential in the regulation of inner mitochondrial permeability and enzyme function by keeping SH in the reduced state. In cisplatin induced toxicity, there is an increase in the intracellular calcium level which activates NADPH oxidase and ROS production by damaged mitochondria (Yao et al., 2007). GSH is one of the most important molecules in the cellular defense against chemically reactive toxic compounds. The reduced form of GSH is necessary for detoxification of xenobiotics. The reduction in GSH levels induced by cisplatin causes suppression of antioxidant enzyme defense system sensitizing the cells to ROS, thus causing hepatic injury (Mansour et al., 2006; Nasr, 2014 and Ciftci et al., 2017).

Nicotinamide adenine dinucleotide (NADH), which helps to maintain SH groups, declines with cisplatin treatment resulting in the inhibition of some dehydrogenases, which cause uncoupling of oxidative phosphorylation with formation hydroxyl radical and oxidative stress. These free radicals attack polyunsaturated lipids and proteins and initiate lipid peroxidation. (Aggarwal, 1998 and Yilmaz, et al., 2005).

The drug is also involved in the alteration of the thiol status of tissue resulting in the alteration in the enzymatic antioxidants. The intracellular redox homeostasis is maintained by the thiol group (-SH) containing molecules. Under certain conditions, thiol group may lead to formation of thiol radicals that in turn interacts with molecular oxygen, generating reactive oxygen species (Desoize, 2002).

The antioxidants play an important role in protection against damage caused by reactive oxygen species (ROS). Reduction in the antioxidant enzyme levels in the current study could be attributed to their utilization in elimination of excess of reactive oxygen species generated during cisplatin toxicity. Bilgic et al., (2018) indicated that in CP induced hepatotoxicity, liver cells encounter large quantities of ROS which overwhelm their detoxification capacity and succumb to toxic effects with depletion of antioxidants. Under normal conditions, protection against ROS is by utilization of NADPH by glutathione reductase to maintain the reduced state of cellular glutathione which is an
important cytosolic antioxidant.

The observations of the study concurred with previous studies which have demonstrated involvement of oxidative stress, lipid peroxidation and mitochondrial dysfunction in cisplatin induced hepatotoxicity (Mansour et al., 2006; Fasihi et al., 2012; Karale and Kamath, 2016 and Ciftci et al., 2017).

Administration of ethanolic extract of Andrographis paniculata ameliorated the deleterious effects of CP which was reflected by significant recovery (P<0.05) in the levels of SOD, GPx and CAT in the animals of Group-IV and Group-V (Tables 1,2,3 and Figure 1, 2, 3) and also by significant reduction (P<0.05) in the levels of MDA (Table 4 and Figure 4). Improvement in the levels of antioxidants [P<0.05] and MDA (P<0.05) was significant in the AP pretreated group [Group-IV] when compared to concurrent AP treatment group [Group-V]. These finding indicating the protective and antioxidant effect of AP against CP which could be attributable to presence of phytochemicals like diterpenoids, flavonoids, tannins, saponins and andrographolides (Verma et al., 2019). The inhibitory effect of Andrographis paniculata on chemically induced cytotoxicity, lipid peroxidation and oxidative stress has been reported in CCl4, benzene hexachloride, paracetamol, and galactosamine induced hepatic damage (Akbar, 2011). The hepatoprotective effect of diterpenes of Andrographis paniculata have been attributed to prevention of oxidation, inhibition of P450 enzymes, stimulation of hepatic regeneration and inhibition of microsomal enzymes and lipid peroxidation (Verma et al., 2019).

The results of the current study suggest that single dose of cisplatin at 7.5 mg/kg intraperitoneally induces oxidative stress in Wistar albino rats by decreasing the cellular endogenous antioxidants enzymes thereby increases the MDA levels and Andrographis paniculata can ameliorate the toxic effects of cisplatin in rats and pretreatment of AP is more effective in comparison with concurrent treatment.

**Table 1** The mean (±SE) values of superoxide dismutase (SOD) levels (U/min/mg protein) in liver of rats in different groups at different time intervals.

| Groups                  | Days post treatment |
|-------------------------|---------------------|
|                         | 07<sup>th</sup>     | 14<sup>th</sup> | 28<sup>th</sup> | 45<sup>th</sup> |
| Group-I                 |                     |                   |                   |                   |
| Negative control        | 28.32±0.05<sup>ax</sup> | 29.35±0.04<sup>ax</sup> | 30.70±0.15<sup>ay</sup> | 31.60±0.42<sup>az</sup> |
| Group-II                |                     |                   |                   |                   |
| CP control              | 9.57±0.13<sup>bx</sup> | 13.57±0.13<sup>by</sup> | 14.74±0.04<sup>bz</sup> | 16.03±0.23<sup>bw</sup> |
| Group-III               |                     |                   |                   |                   |
| AP Control              | 31.60±0.15<sup>ax</sup> | 30.90±0.04<sup>ax</sup> | 31.94±0.03<sup>ax</sup> | 33.90±0.08<sup>ay</sup> |
| Group-IV                |                     |                   |                   |                   |
| AP pre-treatment group  | 19.96±0.03<sup>cx</sup> | 21.82±0.05<sup>cy</sup> | 23.94±0.03<sup>cz</sup> | 24.86±0.25<sup>cw</sup> |
| Group-V                 |                     |                   |                   |                   |
| AP concurrent group     | 13.06±0.01<sup dx</sup> | 14.36±0.08<sup dy</sup> | 20.27±0.01<sup dz</sup> | 20.83±0.08<sup dz</sup> |

Values with different superscripts in a row and column vary significantly at p<0.05
**Table 2** The mean (±SE) values of catalase (μmol/min/mg protein) levels in liver of rats in different groups at different time intervals

| Groups              | Days post treatment | 07th       | 14th       | 28th       | 45th       |
|---------------------|---------------------|------------|------------|------------|------------|
| Group-I Negative control |                     | 50.79±0.139<sup>ax</sup> | 49.52±0.22<sup>ay</sup> | 52.81±0.17<sup>az</sup> | 52.37±0.30<sup>az</sup> |
| Group-II CP control  |                     | 26.57±0.115<sup>bx</sup> | 26.05±0.1<sup>bx</sup> | 27.84±0.07<sup>by</sup> | 30.19±0.50<sup>bz</sup> |
| Group-III AP Control |                     | 51.77±0.09<sup>ax</sup> | 50.02±0.23<sup>ay</sup> | 50.44±0.01<sup>ay</sup> | 53.13±0.11<sup>az</sup> |
| Group-IV AP pre-treatment group |             | 39.09±0.24<sup>cx</sup> | 40.38±0.04<sup>cy</sup> | 42.40±0.05<sup>cz</sup> | 44.76±0.19<sup>cw</sup> |
| Group-V AP concurrent group |                 | 30.99±0.03<sup>dx</sup> | 32.49±0.04<sup>dy</sup> | 33.09±0.04<sup>dz</sup> | 36.36±0.62<sup>dw</sup> |

Values with different superscripts in a row and column vary significantly at p<0.05

**Table 3** The mean (±SE) values of glutathione peroxidase (GPx) levels (U/mg protein) in liver of rats in different groups at different time intervals

| Groups              | Days of post treatment | 07th       | 14th       | 28th       | 45th       |
|---------------------|------------------------|------------|------------|------------|------------|
| Group-I Negative control |                       | 32.15±0.25<sup>ax</sup> | 30.89±0.08<sup>ay</sup> | 32.915±0.16<sup>ax</sup> | 33.96±0.06<sup>ax</sup> |
| Group-II CP control  |                       | 10.78±0.06<sup>bx</sup> | 12.93±0.03<sup>by</sup> | 15.5±0.1<sup>bz</sup> | 15.88±0.16<sup>bz</sup> |
| Group-III AP Control |                       | 32.96±0.15<sup>ax</sup> | 32.61±0.07<sup>ax</sup> | 33.93±0.05<sup>ay</sup> | 34.47±0.18<sup>az</sup> |
| Group-IV AP pre-treatment group |                | 25.96±0.06<sup>cx</sup> | 26.92±0.02<sup>cy</sup> | 27.69±0.03<sup>cw</sup> | 28.79±0.20<sup>cw</sup> |
| Group-V AP concurrent group |                 | 15.58±0.014<sup>dx</sup> | 16.79±0.05<sup>dy</sup> | 20.315±0.06<sup>dz</sup> | 22.14±0.07<sup>dw</sup> |

Values with different superscripts in a row and column vary significantly at p<0.05

**Table 4** The mean (±SE) values of malondialdehyde (MDA) levels (n moles/mg tissue) in liver of rats in different groups at different time intervals

| Groups              | Days post treatment | 07th       | 14th       | 28th       | 45th       |
|---------------------|---------------------|------------|------------|------------|------------|
| Group-I Negative control |                   | 0.98±0.03<sup>ax</sup> | 1.045±0.04<sup>ax</sup> | 1.025±0.014<sup>ax</sup> | 1.00±0.02<sup>ax</sup> |
| Group-II CP control  |                     | 3.595±0.07<sup>bx</sup> | 4.885±0.06<sup>by</sup> | 5.86±0.06<sup>bz</sup> | 4.6±0.17<sup>bz</sup> |
| Group-III AP Control |                     | 0.91±0.03<sup>ax</sup> | 0.9375±0.02<sup>ax</sup> | 1.021±0.02<sup>ay</sup> | 0.939±0.04<sup>ax</sup> |
| Group-IV AP pre-treatment group |            | 3.0±0.01<sup>cx</sup> | 3.72±0.04<sup>cy</sup> | 3.285±0.01<sup>cw</sup> | 2.47±0.19<sup>cw</sup> |
| Group-V AP concurrent group |                 | 3.16±0.09<sup>cx</sup> | 4.05±0.03<sup>cy</sup> | 3.57±0.01<sup>dx</sup> | 3.11±0.06<sup>dx</sup> |

Values with different superscripts in a row and column vary significantly at p<0.05
**Figure 1** The mean (±SE) values of superoxide dismutase (SOD) levels (U/min/mg protein) in liver of rats in different groups at different time intervals.

**Figure 2** The mean (±SE) values of catalase (μmol/min/mg protein) levels in liver of rats in different groups at different time intervals.

**Figure 3** The mean (±SE) values of glutathione peroxidase (GPx) levels (U/mg protein) in liver of rats in different groups at different time intervals.
**Figure 4** The mean (±SE) values of malondialdehyde (MDA) levels (n moles/mg tissue) in liver of rats in different groups at different time intervals

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