Effect of *Gymnema Sylvestre* Leaf Extract on Neurotoxicity Caused by Cisplatin in Male Albino Rats

Doaa S. Ibrahim (✉ Doaa.mohamed@fsc.bu.edu.eg)

Benha University Faculty of Science <https://orcid.org/0000-0002-5882-0832>

Research Article

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Abstract

Gymnema sylvestre (*G. sylvestre*), commonly known as gurmar, is famous for containing bioactive compounds which made it eligible for use as a medicinal plant. Therefore, the purpose of this study was to investigate the potential of *G. sylvestre* leaf extract in improving the neurotoxic effect of cisplatin (CP). Five groups of rats (6 rats each) were divided into the control group, the gurmar group (administrated orally 100 mg/kg bw), the CP group (received a single intraperitoneal injection of 5 mg/kg bw), the CP + gurmar group, and the gurmar + CP group. After 12 days (the experiment period), the brains of rats were removed and stored to evaluate biochemical parameters. CP injection led to elevated levels of malondialdehyde (MDA), nuclear factor-kappa B (NF- κ B), tumor necrosis factor-alpha (TNF- α), and apoptosis (caspases 8, 9, and 12) and decreasing the activities of antioxidant enzymes (catalase and superoxide dismutase) and neurotrophins (nerve growth factor and brain-derived neurotrophic factor) levels in brains of rats. On the other hand, administration of *G. sylvestre* leaf extract decreased MDA, NF- κ B, TNF- α , and apoptosis levels and increased antioxidant enzymes activities and neurotrophins levels in the brains of rats injected by CP. This study demonstrated the ability of *G. sylvestre* leaf extract to counteract the neurotoxicity induced by CP through the antioxidant, anti-inflammatory, and anti-apoptotic activities shown by *G. sylvestre* leaf extract.

Introduction

Neurotoxicity is the damage caused to the nervous system when exposed to a toxic substance (Spencer and Lein, 2014). Chemotherapeutic drugs are known for their toxicity on the nervous system (Nielsen and Brant, 2002). CP one of the most widely used chemotherapeutic drugs is associated with ototoxicity and neurotoxicity (dos Santos et al., 2020). CP is composed of a central atom of platinum surrounded by two chloride molecules and two ammonia molecules (Dasari and Tchounwou, 2014). Mehmood (2014) reported that the platinum atom of CP is irreversibly bound to plasma proteins (albumin, transferrin, and gamma globulin). After that CP can cross the blood-brain barrier and penetrate the brain (Jacobs et al., 2010). CP induces neurotoxicity by several mechanisms including oxidative stress, inflammation, DNA damage, and apoptosis (Almutairi et al., 2017). Oxidative stress is considered the main way that taken by CP to cause neurotoxicity (Asensio-Lopez et al., 2017). Where CP raises free radicals and reduces the antioxidant enzymes (Yadav, 2019).

G. sylvestre, a woody climber plant, is widely used as a traditional medicine in Asia, Africa, and Australia (Fatani et al., 2015). It has been traditionally used in treating diabetes, malaria, snake bite, dyspepsia, constipation, jaundice, hemorrhoids, renal and vesicle calculi, cardiopathy, asthma, bronchitis, amenorrhea, and leucoderma (Khan et al., 2019). Many previous studies confirmed that leaves of *G. sylvestre* contain many phytochemical compounds like alkaloids, flavonoids, saponins (Gopinath et al., 2012), gymnemic acids (Tiwari et al., 2014), acidic glycosides, anthraquinones, flavones, hentriacontane, pentatriacontane, phytin, resins, tartaric acid, formic acid, butyric acid, lupeol and β -amyrin (Pagadala et al., 2015).

Therefore, the purpose of this study was to clarify the role of *G. sylvestre* leaf extract in improving the neurotoxicity of cisplatin.

Materials And Methods

Cisplatin and *G. sylvestre* leaf extract:

CP purchased from Sigma Company (Sigma-Aldrich Louis, MO, USA) was injected as a single intraperitoneal dose (5 mg/kg bw) according to Abdel Moneim (2014). The CP injection dose was selected after knowing the lethal dose 50 (LD50) for CP in rats which was 12 mg/kg body weight according to Abas (2017).

G. sylvestre leaf extract was obtained from the Arab Company for Pharmaceuticals and Medicinal Plants (MEPACO, Egypt) as a gift. Previous phytochemical studies on the same extract purchased from the same company revealed the presence of several gymneric acids as the main component besides anthraquinones and their derivatives present in the extract (Al-Rejaie et al., 2012 & Aleisa et al., 2014). The dose of 100 mg/kg bw of *G. sylvestre* leaf extract has been selected according to Fatani *et al.* (2015) based on the acute toxicity study done by Raji et al. (2021)

Animals

Thirty male Wistar albino rats (weighing 170 ± 10 g) were purchased from the Helwan Farm of the Egyptian Organization for Vaccine and Biological Preparations (VACSERA, Cairo, Egypt). Rats were acclimatized under standard laboratory conditions ($25 \pm 2^\circ\text{C}$, 12 hours light/dark cycle, and given food and water ad libitum) for 7 days before the beginning of the experiment. The present study was approved by the Zoology Department, Faculty of Science, Benha University - (IACUC) which is registered with the Egyptian Network of Research Ethics Committees (Approval No. ZD/FSc/BU- 2021-3).

Experimental design

Rats were divided randomly into five groups (six rats each) as follows; the control group, the gurmar group (rats administrated *G. sylvestre* leaf extract for 12 days), the CP group (rats injected with cisplatin), the CP + gurmar group (rats injected with cisplatin then after 5 days treated with a daily oral dose of *G. sylvestre* leaf extract for 7 days), and the gurmar + CP group (rats administrated a daily oral dose of *G. sylvestre* leaf extract for 7 days then injected with cisplatin).

Samples preparation

After 12 days (the experiment period), the overnight fasting animals were anesthetized (inhalation of diethyl ether). Brains were immediately removed and then were washed and homogenized in ice-cold phosphate buffer saline (PBS, pH 7.2). After centrifugation (5000 xg for 5 min) the clear supernatant was stored at -20°C to be used for biochemical analysis.

Biochemical assays

In the brain tissues, malondialdehyde (MDA) content was measured using a competitive ELISA assay, catalase (CAT) activity was determined by a colorimetric/fluorometric assay, and superoxide dismutase activity (SOD) activity was determined by using a sandwich ELISA assay. All the above assay kits have been purchased from BioVision, Inc. (CA, USA).

Neuronal nuclear factor-kappa B (NF- κ B) and tumor necrosis factor-alpha (TNF- α) levels were measured by using sandwich ELISA assay (Abbexa Ltd., Cambridge, UK and BioVision, CA, USA, respectively).

Brian apoptosis (caspases 8, 9, and 12) levels were determined by sandwich ELISA rat kits purchased from the MyBioSource (San Diego, CA, USA).

Nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) in the supernatants of homogenated brains were measured according to Fiore et al (2009) and Binder and Scharfman (2004), respectively using MyBioSource (San Diego, CA, USA) rat ELISA kits.

Statistical analysis

The result of each group was expressed as the mean $\pm$ standard deviation. For the comparison of significance between groups, the computer program Statistical Package for Social Science (SPSS, Version 20.00, Chicago, USA) was used for performing a one-way analysis of variance (ANOVA) followed by Duncan's multiple range test. Statistical significance was set at $P < 0.05$.

Results

Effect of *G. sylvestre* leaf extract on neuronal oxidative stress parameters

Table (1) showed a significant decrease ($P < 0.05$) in neuronal MDA content and marked increases in neuronal antioxidant enzymes (CAT and SOD) activities in the gurmar group compared to the control group. CP induction caused a significant increase in neuronal MDA content and significant decreases in neuronal antioxidant enzymes activities compared to the control group. While administration of gurmar leaf extract declined the neuronal MDA content and elevated the neuronal antioxidant enzymes activities in brains of rats injected with CP. Of note, the gurmar + CP group improved the oxidative stress parameters more than the CP + gurmar group.

Effect of *G. sylvestre* leaf extract on neuronal NF- κ B and TNF- α levels

As shown in Table 2, the neuronal NF- κ B and TNF- α levels were decreased markedly ($P < 0.05$) after gurmar leaf extract administration when compared with the control group. The CP group showed obvious increases in neuronal NF- κ B and TNF- α levels, whereas the gurmar groups that were injected with CP showed significant decreases in neuronal NF- κ B and TNF- α levels compared to the CP group and that improvements in the neuronal NF- κ B and TNF- α levels were clear in the gurmar + CP group than the CP + gurmar group.

Table 1

Effects of gurmar (*Gymnema sylvestre*) leaf extract (100 mg/kg bw) on oxidative stress parameters in brains of rats injected with cisplatin (5 mg/kg bw).

	Groups				
	Control	Gurmar	Cisplatin	Cisplatin+gurmar	Gurmar+cisplatin
MDA (ng/g tissue)	8.57±0.07 ^d	8.05±0.05 ^e	31.47±0.16 ^a	25.77±0.18 ^b	22.61±0.10 ^c
CAT (mU/g tissue)	20.97±0.12 ^b	25.49±0.22 ^a	7.92±0.06 ^e	12.58±0.09 ^d	13.81±0.08 ^c
SOD (ng/g tissue)	25.12±0.27 ^b	29.21±0.61 ^a	11.64±0.25 ^e	16.71±0.62 ^d	17.65±0.64 ^c
All data expressed as mean ± standard deviation.					
Values with different letters in the same row were significantly different ($P < 0.05$).					

Table 2

Effects of gurmar (*Gymnema sylvestre*) leaf extract (100 mg/kg bw) on nuclear factor-kappa B (NF-κB) and tumor necrosis factor-alpha (TNF-α) levels in brains of rats injected with cisplatin (5 mg/kg bw).

	Groups				
	Control	Gurmar	Cisplatin	Cisplatin+gurmar	Gurmar+cisplatin
NF-κB (ng/g tissue)	0.51±0.05 ^d	0.43±0.03 ^e	3.54±0.15 ^a	3.01±0.13 ^b	2.92±0.11 ^c
TNF-α (pg/g tissue)	101.36±2.70 ^d	95.47±2.87 ^e	167.58±3.85 ^a	147.91±2.96 ^b	140.33±3.04 ^c
All data expressed as mean ± standard deviation.					
Values with different letters in the same row were significantly different ($P < 0.05$).					

Effect of *G. sylvestre* leaf extract on neuronal apoptosis parameters

Compared with the control group, there were significant decreases ($P < 0.05$) in renal caspases-8 level in the gurmar group. Meanwhile, the CP group recorded marked elevation in neuronal apoptosis parameters (caspases 8, 9 and 12) in comparison to the control group. The gurmar groups injected with CP showed low levels of neuronal apoptosis in comparison to the CP group. Moreover, the gurmar + CP group showed low levels of neuronal apoptosis compared to the CP + gurmar group (Table 3).

Table 3

Effects of gurmar (*Gymnema sylvestre*) leaf extract (100 mg/kg bw) on apoptosis parameters in brains of rats injected with cisplatin (5 mg/kg bw).

	Groups				
	Control	Gurmar	Cisplatin	Cisplatin+gurmar	Gurmar+cisplatin
Caspase-8 (ng/g tissue)	0.49±0.04 ^d	0.43±0.02 ^e	3.19±0.09 ^a	3.08±0.08 ^b	3.05±0.06 ^c
Caspase-9 (ng/g tissue)	0.37±0.02 ^d	0.36±0.01 ^d	2.23±0.04 ^a	2.17±0.06 ^b	2.06±0.05 ^c
Caspase-12 (ng/g tissue)	0.48±0.03 ^d	0.47±0.01 ^d	2.58±0.08 ^a	2.49±0.02 ^b	2.44±0.03 ^c
All data expressed as mean ± standard deviation.					
Values with different letters in the same row were significantly different ($P < 0.05$).					

Effect of *G. sylvestre* leaf extract on neurotrophins levels

In gurmar group, the neurotrophins (NGF and BDNF) levels in the brains of rats increased markedly ($P < 0.05$) compared to the control group. Rats injected with CP showed significant reductions in brain tissues neurotrophins levels. While levels of neurotrophins in the brains of rats increased markedly in gurmar administered groups compared to the CP group and that increase was markedly clear in the gurmar + CP group than the CP + gurmar group (Table 4).

Table 4

Effects of gurmar (*Gymnema sylvestre*) leaf extract (100 mg/kg bw) on neurotrophins levels in brains of rats injected with cisplatin (5 mg/kg bw).

	Groups				
	Control	Gurmar	Cisplatin	Cisplatin+gurmar	Gurmar+cisplatin
NGF (pg/g tissue)	85.44±1.50 ^b	89.21±1.79 ^a	25.47±1.31 ^e	26.05±1.20 ^d	83.07±1.34 ^c
BDNF (pg/g tissue)	171.01±2.00 ^b	182.41±2.79 ^a	45.88±1.31 ^e	46.79±1.43 ^d	166.29±2.06 ^c
All data expressed as mean ± standard deviation.					
Values with different letters in the same row were significantly different ($P < 0.05$).					

Discussion

CP has been known for its neurotoxicity, which has been recorded by several studies (Attia et al., 2021). Oxidative stress is considered the main reason for the neurotoxicity of CP (Abdel-Wahab and Moussa, 2019). As the effect of CP is not limited to the production of free radicals only but also the depletion of neural antioxidant enzymes (Yadav, 2019). The oxidative stress associated with CP was clear in this study through the marked increase in MDA level (ROS indicator) and the significant decrease in antioxidant enzymes (SOD and CAT) activities in rats' brains. This result is consistent with a previous study (Attia et al., 2021), which reported that administration of CP caused high lipid peroxidation levels and low SOD and glutathione peroxidase (GPx) activities in mice brains. In addition, CP decreased the SOD activity by losing copper and zinc which are essential for SOD activity (Abdel Moneim, 2014).

The present study proved the antioxidant activity of *G. sylvestre* leaf extract as it decreased MDA level and increased antioxidant enzymes activities in rat brains injected with CP. This may be attributed to the antioxidant components of the *G. sylvestre* leaf extract. Previous phytochemical studies that occurred on *G. sylvestre* extract have revealed the presence of bioactive compounds (flavonoids, phenols, various gymnemic acid, gymnemarin, saponins, tannins, and triterpenoids) that provided *G. sylvestre* by its antioxidant activity (Senthilkumar, 2015 & Laha and Paul, 2019). Moreover, Khan et al. (2019) suggested that the antioxidant activity of *G. sylvestre* might be due to its ability to scavenge hydrogen peroxide, nitric oxide, and superoxide radically induced oxidative stress in rats.

Neuroinflammation is one of the ways used by CP in inducing neurotoxicity (Abdel-Wahab and Moussa, 2019). Sadhukhan et al. (2018) and Gao et al. (2021) mentioned that the high levels of reactive oxygen species associated with cisplatin injection activate NF- κ B that is translocated into the nucleus where it activates the transcription of various pro-inflammatory cytokines such as TNF- α . The current study recorded high levels of NF- κ B and TNF- α which confirmed the occurrence of neuroinflammation by CP.

Administration of *G. sylvestre* leaf extract markedly decreased NF- κ B and TNF- α levels in brains of rats injected with CP that confirmed the anti-inflammatory activity of *G. sylvestre* leaf extract that attributed to its antioxidant activity. In support of this view, Kumar et al. (2012) reported that *G. sylvestre* extract has anti-inflammatory activity in rats treated with carrageenan. Also, Aleisa et al. (2014) confirmed the anti-inflammatory and antioxidant activities of *G. sylvestre* against colitis. The presence of tannins and saponins in *G. sylvestre* are responsible for its anti-inflammatory activity (Gupta et al., 2010 & Tiwari et al., 2014). Moreover, Uivaros *et al.* (2010) reported that flavonoids have anti-inflammatory and neuroprotective properties. Fatani *et al.* (2015) attributed the anti-inflammatory effect of *G. sylvestre* leaf extract in diabetic neuropathy to its ability to inhibit NF- κ B activation.

Apoptosis is considered one of the most important ways of CP for causing neurotoxicity (Rathinam et al., 2015). CP causes apoptosis by activation several caspases, a family of cysteine aspartate proteases (Seki et al., 2000). It was reported that CP activates caspase-8 by binding to the death receptors on the plasma membrane (dos Santos et al., 2012). Moreover, CP also activates caspase-9 via activation Bax and Bak (Dugbartey et al., 2016). In addition, CP interacts with cytochrome P450 on the endoplasmic

reticulum membrane and induces oxidative stress that activates caspase-12 (Fang et al., 2021). Activation of the initiator caspases (caspases-8, 9, and 12) leads to activating downstream caspases and induces apoptosis (Liu and Baliga, 2005). The neuronal apoptosis of CP was confirmed in the current study through the high levels of initiator caspases (caspases-8, 9, and 12).

Our data reported that *G. sylvestre* leaf extract blocked the three apoptosis pathways induced by CP in brain tissue by inhibiting the initiator caspases (caspases-8, 9, and 12) levels. *G. sylvestre* leaf extract might inhibit apoptosis induced by CP by improving the oxidative stress and increasing the neurotrophins (NGF and BDNF) expression. Gomaa et al. (2020) reported that the increase of BDNF expression up-regulates some anti-apoptotic proteins and blocks apoptotic markers such as caspase-3, thus promoting neuronal regeneration. Kumar et al (2013) also proved the anti-apoptotic potential of *G. sylvestre* leaf extract in STZ-induced diabetic cardiomyopathy. Gymnemic acid, one of *G. sylvestre* leaf extracts mixed with phospholipid has an anti-apoptotic effect on cardiotoxicity in rats (Pathan et al., 2012). Fang et al. (2021) proved that saponins have anti-apoptotic activity against the renal damage induced by CP.

Neurotrophic factors (neurotrophins) are a group of growth factors consisting of NGF, BDNF, NT3, and NT4 (Meng et al., 2019). To initiate cell survival, NGF and BDNF must bind to tropomyosin receptor kinase (Trk) A and B, respectively (Weissmiller and Wu, 2012). NGF and BDNF activation promote neuroprotection, synaptogenesis, and neurogenesis (Chung et al., 2020). Winocur et al. (2015) reported that CP caused neuronal loss via activation of neuronal apoptosis and inhibition of neurogenesis. In the present study, CP markedly reduced levels of neurotrophins (NGF and BDNF) in the brains of rats, indicating a loss of neural integrity and an increased apoptotic neuronal death. Aloe et al. (2000) attributed the downregulating of NGF or NGF receptors' synthesis to the binding of CP to DNA. While Gomaa et al. (2020) reported that CP decreased BDNF expression via reduction cerebral XIAP concentration that inhibited the phosphorylation of the TrkB receptor (one of the most important membrane receptors of BDNF).

Administration *G. sylvestre* leaf extract increased brain tissue NGF and BDNF levels in rats injected with CP and that might be explained due to the efficiency of *G. sylvestre* leaf extract to scavenge the free radicals and increase the activity of antioxidant activities. This result agrees with Fatani *et al.* (2015) who proved that *G. sylvestre* leaf extract elevation of sciatic tissue levels of IGF and NGF in the diabetic rats

The results of this study demonstrated for the first time the success of *G. sylvestre* leaf extract in reducing the neurotoxicity caused by CP. This success is due to the antioxidant, anti-inflammatory, and anti-apoptotic abilities shown by *G. sylvestre* leaf extract. And not only that, but *G. sylvestre* leaf extract was also able to raise levels of neurotrophins in rats injected by CP.

Declarations

Ethical Approval: The present study was approved by the Zoology Department, Faculty of Science, Benha University - (IACUC) which is registered with the Egyptian Network of Research Ethics Committees (Approval No. ZD/FSc/BU- 2021-1).

Consent to Participate: Not applicable.

Consent to Publish: Not applicable.

Authors Contributions: Not applicable.

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Competing Interests: The authors declare no competing interests.

Availability of data and materials: All data are mentioned in the body of manuscript, tables, and figure.

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Figures

Figure 1

Effects of *G. sylvestre* leaf extract (100 mg/kg bw) on final body weight in cisplatin (5 mg/kg bw)-induced neurotoxicity in rats. Different letters mean statistically significant differences ($P < 0.05$).