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The Neuroprotective Effects of Simvastatin in Doxorubicin-Induced Brain Toxicity in Rats

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Abstract

Lipophilic statins (e.g., simvastatin (SMV)) played a cytoprotective role against various injuries via mitigating neuroinflammation and attenuating oxidative damage. Doxorubicin (Dox) leads to tissue injury, particularly cardiotoxicity and brain toxicity. The present study aimed to investigate the neuroprotective potential of SMV against Dox-induced neurotoxicity in rats. A total of 56 Albino Wistar rats were housed in cages and subclassified into control male and female groups, Dox male and female groups, SMV male and female groups, and SMV+Dox male and female groups. The brain tissue samples for all groups were harvested at day 16 and assessed through histological examination. The scoring results of these rats' brain sections indicated that control groups demonstrated normal histology (scoring 0), SMV groups associated with mild congestion in both sexes; mild demyelination only in females (scoring 1), Dox group demonstrated severe histopathology (scoring 3), and the combination of SMV+Dox demonstrated a notable reduction in histopathology scoring (Scores 0-1). The outcomes of the present study provided clear evidence that SMV provided marked neuroprotection against Dox-induced neurotoxicity in both male and female rats.

Keywords: Brain, Chemobrain, Doxorubicin, Simvastatin, Neuroprotection

Introduction

Doxorubicin (Dox) is an anthracycline antibiotic employed in clinical oncology for its efficacious chemotherapeutic effects against breast cancer, leukaemia, lymphoma, sarcomas, and solid tumours (Bárdi *et al*., 2007; Ichikawa *et al*., 2014). The antineoplastic mechanism of Dox is primarily based on intercalation into DNA, blocking of topoisomerase II, and production of free radicals that stimulate DNA damage and lipid peroxidation, eventually leading to cancer cell death (Ichikawa *et al*., 2014; Vitale *et al*., 2024; Ito-Hagiwara *et al*., 2025). Nonetheless, the therapeutic efficacy of Dox is counteracted by dose-dependent cardiotoxicity (Shafik *et al*., 2011; Guillen & Pereira, 2024; Kebe *et al*., 2025). Moreover, Dox-containing chemotherapy regimens are also associated with central nervous system (CNS) adverse effects, including cognitive damage, memory deficits, attention insufficiencies, executive dysfunction, and loss of concentration, a collection of symptoms termed "chemo-brain" (Sardi *et al*., 2013). These CNS symptoms may take a long time to resolve, negatively impacting the quality of life in cancer survivors (Aryal *et al*., 2013; Khan *et al*., 2024; Lee *et al*., 2025). Despite being water-soluble and hence unable to cross the intact blood-brain barrier (BBB), Dox indirectly induces CNS toxicity by promoting systemic inflammation, oxidative stress, and mitochondrial dysfunction (Wohlfart *et al*., 2011; Csep *et al*., 2024; Conti *et al*., 2025). These three mechanisms collectively disrupt the BBB integrity, resulting in microglial upset, neuronal apoptosis, disrupting neurogenesis, and impairing white matter integrity (Wallace *et al*., 2020; Snodin & McCrossen, 2024; Njoroge & Odhiambo, 2025).

The large number of cancer survivors with chemobrain necessitates searching for neuroprotective therapy to minimise the chemobrain (Aryal *et al*., 2013; Ganea *et al*., 2024; Raza *et al*., 2025). Statins due to their systemic pleiotropic effects, including antioxidant, anti-inflammatory, and endothelial-protective properties (Bahrami *et al*., 2020; Zar *et al*., 2024; Petchesi *et al*., 2025). Locally inside the CNS, statins mitigate neuroinflammation, attenuate oxidative damage, preserve BBB integrity, and encourage neuronal survival (Liu *et al*., 2024; Mickevičius *et al*., 2024; Yu *et al*., 2025). Interestingly, the lipophilic statins (e.g., simvastatin) cross the BBB and have been shown to exert neuroprotective effects after accumulation in brain tissue (Vuu *et al*., 2023; Yılmazer & Altinok, 2024). Earlier experimental animal studies demonstrated that SMV provided neuroprotection in cerebral ischemia, traumatic brain injury, neurodegenerative diseases, and neuroinflammation, via its antioxidant effects, inhibition of microglial cells, suppression of pro-inflammatory cytokine generation, overexpression of endothelial nitric oxide synthase, leading to increased cerebral blood flow and improved neurotransmission (McGown & Brookes, 2007; Zhang *et al*., 2023). The present study was designed to investigate the histoprotective potential of SMV against Dox-induced neurotoxicity in brain sections

Materials and Methods

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Study setting: The study was officially registered at the College of Pharmacy, University of Mosul (Iraq), registration session number 06 on 05.02.2026.

Animals and housing: 56 Albino Wistar rats (2 months old, average body weight 250g) were housed in cages and acclimatized for 2 weeks under a standard dark/light cycle, with humidity, food, and water provided. The study was conducted in the animal house at the College of Veterinary Medicine, University of Mosul (Iraq).

Experimental design: The 56 rats were subdivided into 8 groups, as outlined in **Table 1**.

Table 1. Experimental design of the studied groups.

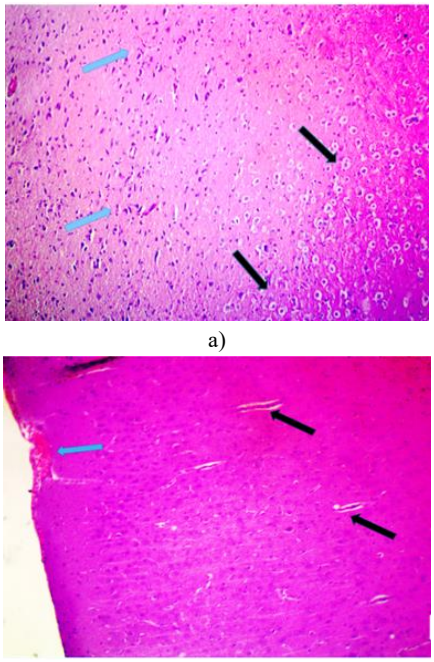
Studied groups	No. rats	distilled water orally for 13 days	Normal saline, IP single dose at day 14	SMV, oral dose 10mg/kg/day for 13	Dox, Single IP dose 15mg/kg at day 14
Control the female group	7	*	*	----	----
Control the male group	7	*	*	----	----
Dox female group	7	*	----	----	*
Dox male group	7	*	----	----	*
SMV female group	7	----	*	*	----
SMV male group	7	----	*	*	----
SMV+Dox female group	7	----	----	*	*
SMV+Dox male group	7	----	----	*	*

day 16, brain tissue harvesting after the animal was sacrificed by cervical spine dislocation.
Drugs and distilled water were given by gavage needle
Dox vial (Doxo-cell 50 mg, STADAPHARM GmbH (Germany)) was diluted for administration using normal saline
Simvastatin tablets (Simvatin 10mg, Aldawlia (Jordan)) were dissolved in distilled water

Histological analysis: The histology of the brain section was analysed after the rats were sacrificed and the brain was harvested. The brain tissue was washed with normal saline and fixed in 10% formalin for 3 days, until all samples were collected for histological analysis. On the day the histological analysis began, the tissue samples were washed with normal saline to remove the fixative. The tissues were then dehydrated by removing moisture through sequential exposure to 70%, 80%, 90%, and 100% alcohol. Alcohol was replaced by xylene to make the tissue receptive to the wax step. The brain tissue sections were placed in liquid paraffin wax in a mould, cooled to solidify, and then cut into thin 5µm slices using a microtome. These slices were then freed into a warmed water bath and then sliced on the slide glass. After drying, the slides were deparaffinized and rehydrated, then stained with Hematoxylin and Eosin (H&E). The tissues were examined under a microscope, and images were taken for each group. The samples were scored by a histopathologist for comparison.

Results and Discussion

The rat brain section of the control group (male or female) revealed normal neurons in the cerebral cortex with no apparent degeneration, necrosis, or cytoplasmic vacuolation. The control group also demonstrated an intact cerebral medulla, as evidenced by the absence of demyelination, oedema, or axonal damage, indicating normal axons with intact periaxonal myelin spaces **(Figure 1)**.

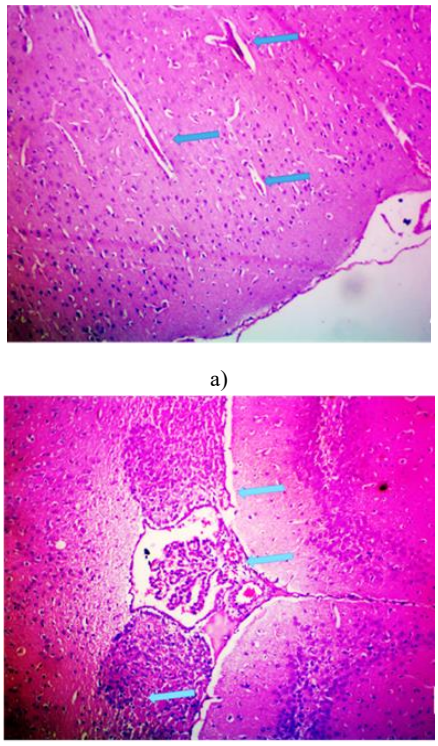


a)

b)

Figure 1. A representative image for rat brain section. (a) female control group showing normal neurons at the cerebral cortex (Blue arrows) and normal axons with normal periaxonal myelin spaces at the cerebral medulla (Black arrows). (b) male control group showing normal neurons at the cerebral cortex (Blue arrows) and normal axons with normal periaxonal myelin spaces at the cerebral medulla (Black arrows). H&E stain, 100X

The rat brain section of the SMV group in females revealed mildly congested cerebral choroid Plexus, reflecting vascular dilation within the choroid plexus **(Figure 2a)**. In contrast, the male group demonstrated only vascular dilation within the choroid plexus **(Figure 2b)**.

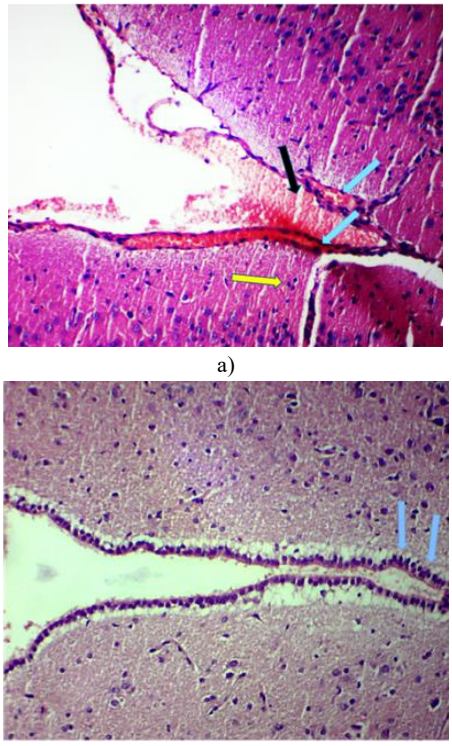


a)

b)

Figure 2. A representative image for rat brain section in the simvastatin. (a) female revealing mild degeneration (Blue arrows). (b) male revealing mild congested cerebral ventricular plexus (Blue arrows) H&E stain, 100X.

The rat brain section of the Dox group in females revealed strong hyperemic meningeal vasculature, presenting as severe vascular congestion in the meninges and focal epidural haemorrhage. Moreover, the CNS injury presented with focal gliosis and damage to astrocytes and microglia **(Figure 3a)**. The rat brain section of the Dox group in males revealed severe hyperplastic ependymal cells, vascular congestion, and focal epidural haemorrhage **(Figure 3b)**.

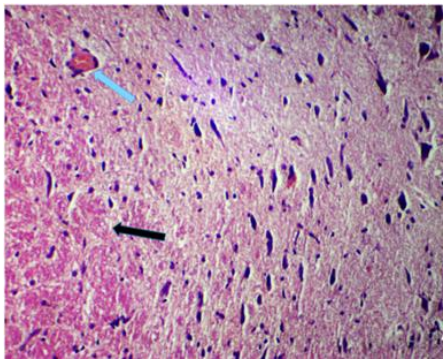


a)

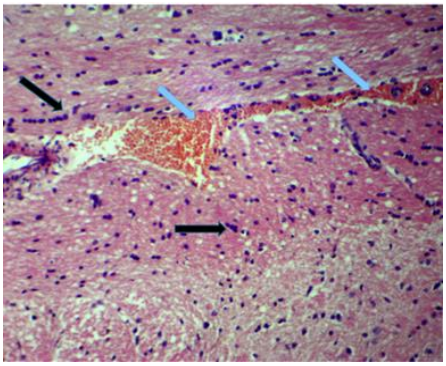
b)

Figure 3. A representative image for rat brain section in the doxorubicin. (a) female revealing exploring hyperemic meningeal arterioles (Blue arrows) , focal epidural hemorrhage (Black arrows) and focal gliosis (Yellow arrows). (b) male showing high hyperplastic ependymal cells (Blue arrows). No focal epidural hemorrhage and no focal gliosis. H&E stain, 100X.

The rat brain section of the SMV+Dox group in females revealed only a loss of myelin sheath and mild vascular congestion **(Figure 4a)**, whereas the male group demonstrated mild vascular congestion and engorgement with blood alongside mild degeneration of neuronal axons **(Figure 4b)**.



a)



b)

Figure 4. A representative image for rat brain section in the simvastatin+doxorubicin (a) female congested cerebral capillary (Blue arrows), mild Wallerian degeneration of neuronal axons (Black arrows). (b) male revealing hyperemic cerebral arteriole (Blue arrows) , intense gliosis or neurophagy of degenerated axons (Black arrows). Staining H&E stain, 100X.

The scoring results of these rats brain section indicated that control groups demonstraed normal histology (scoring 0), SMV groups associated with mild congestion in both sexes; mild demyelination only in females (scoring 1), Dox group demonstrated severe hitopathology (scoring 3), and combination of SMV+Dox demonstrated notable reduction in histopathology scoring (Scores 0-1), **Table 2**.

Table 2. Scoring results of the rat brain section of the studied groups.

Parameters	Figure 1a	Figure 1b	Figure 2a	Figure 2b	Figure 3a	Figure 3b	Figure 4a	Figure 4b
	$Control^F$	$Control^M$	SMV^F	SMV^M	Dox^F	Dox^M	$SMV+Dox^F$	$SMV+Dox^M$
Neuronal Degeneration	0	0	---	0	3	3	0	1
Demyelination	0	0	1	0	3	3	1	1
Vascular Congestion	0	0	1	1	3	3	1	1

The findings of the present study explored the neuroprotective potentials of SMV against Dox-induced neuronal injury in the brain section of insulted rats, with a specific focus on the sex variation in the response of histological protections. The outcomes revealed that Dox induced extensive brain injury in both sexes. At the same time, co-administration of SMV with Dox mitigated these destructive Dox effects on the brain, offering potential neuroprotection in chemotherapy-induced neurotoxicity.

Despite the low penetration capacity of Dox, however, the neurotoxicity present (Wohlfart *et al*., 2011; Sardi *et al*., 2013; Jagsi *et al*., 2025), due to indirect Dox toxicity through oxidative stress, pro-inflammatory cytokine generation, and endothelial injury (Shi *et al*., 2023; Dupont & Lefevre, 2024; Vitale *et al*., 2024). Female rats treated with Dox demonstrated vascular congestion, epidural haemorrhage, and focal gliosis, whereas male rats treated with Dox demonstrated enlargement of ependymal cells, vascular congestion, and epidural haemorrhage (Mohamed *et al*., 2011; Aryal *et al*., 2013; Elamin *et al*., 2023; Abdelsalam, 2024; Kowalski *et al*., 2024). ependymal cell hyperplasia, which is distinctively demonstrated in males, potentially reflecting a proliferative nature response to ventricular system inflammation (Elmore *et al*., 2013). Vascular congestion in the brain meninges and choroid plexus associated with Dox, leading to diminished cerebral perfusion, is described as a "chemo-brain (Siegal *et al*., 1988; Johanson *et al*., 2011; Pardo-Zamora & Castellano-Rioja, 2024).

Histopathological changes in rats associated with the use of SMV alone were mild in both sexes and were exclusively associated with mild demyelination (Siegal *et al*., 1988; Miron *et al*., 2009; Johanson *et al*., 2011; Maslyakova *et al*., 2023). This effect is potentially associated with the impact of SMV on cholesterol synthesis, critical for myelin support (Holmberg *et al*., 2006; Cibičková *et al*., 2008; Salem *et al*., 2025), even though the lack of neuronal degeneration has confirmed SMV safety (Ramirez *et al*., 2011; Vuu *et al*., 2023). The administration of SMV with Dox led to attenuation of Dox-induced neurotoxicity in both sexes, represented by a reduced neurotoxicity score of 3 down to 1, reaching a near normal value of control and SMV alone regarding neuronal degeneration, demyelination, and vascular congestion, with a preferable role in females compared to males. The neuroprotective mechanism of SMV is multifactorial and indirect, including antioxidant, anti-inflammatory, and endothelial protection, preserving neuronal cellular integrity (Wang *et al*., 2014; Barna *et al*., 2020; Liu *et al*., 2024; Leadbeatter & Tjaya, 2024). Additionally, SMV encourages the production of endothelial nitric oxide, correcting microvascular congestion and improving the vascular function (Mital *et al*., 2000; McGown & Brookes, 2007; Gorabi *et al*., 2019). Finally, SMV improved neuroinflammation by reducing microglial stimulation and blocking cytokine synthesis and release, attenuating gliosis, as investigated in the current study (Li *et al*., 2009; Zheng *et al*., 2018; Bagheri *et al*., 2020).

The sex provided distinct outcomes on certain aspects, with more demyelination expressed in females compared to males in all groups, whereas males expressed ependymal cell hyperplasia after exposure to Dox. These variations could potentially reflect the estrogen role in modulating statin pharmacokinetics and Dox responses.

Conclusion

The outcomes of the present study offered clear evidence that SMV provided marked neuroprotection against Dox-induced neurotoxicity in rats, via mitigating neurodegeneration, demyelination, and vascular dilation in both sexes.

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Conflict of interest: None

Financial support: None

Ethics statement: The study approved and registered at Scientific Committee in the College of Pharmacy at University of Mosul (Approval Number session 06 on 02.02.2026).

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