The survey effect of melatonin on the testicular toxicity induced by the bleomycin, etoposide and cisplatin (BEP) regimen in rat administration

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Introduction

There is growing concern that some cytotoxic regimens for cancer adversely affect spermatogenesis and male fertility. Increasing evidence demonstrated that melatonin has beneficial impacts on reproductive processes; however, whether melatonin can protect against bleomycin, etoposide, and cisplatin (BEP) chemotherapy regimen-induced testicular toxicity, remains obscure. The present study aimed to explore the effect of melatonin on BEP-evoked testicular injury in rats.

Methods

Adult male Wistar rats (n = 10/group) were intraperitoneally (i.p.) injected with one cycle of 21 days of 0.33 therapeutically relevant dose levels of BEP (.5 mg/kg bleomycin, 5 mg/kg etoposide, and 1 mg/kg cisplatin) with or without melatonin. At the end of the study, sperm parameters, testosterone level, stereology of testes, testicular levels of malondialdehyde (MDA), nitric oxide (NO), and total antioxidant capacity (TAC), the expression of apoptosis-associated genes such as Bcl2, Bax, Caspase-3, p53, and TNF-α (Real-time PCR and Immunohistochemistry) were evaluated.

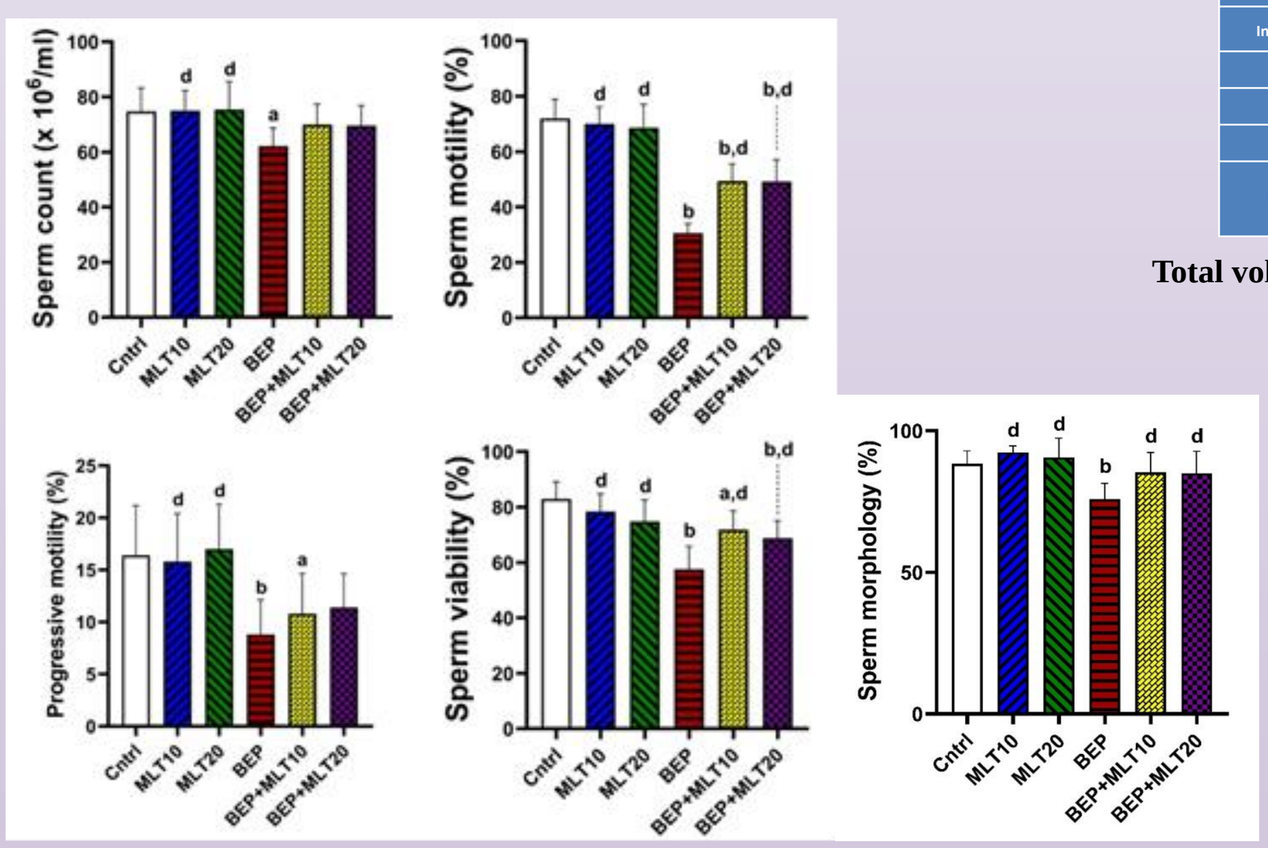
Our findings showed that melatonin restored spermatogenesis by improving sperm count, motility, viability, and morphology. Testosterone level, histopathology, and stereology of testes were significantly improved in melatonin-administrated groups. Furthermore, melatonin recovered the oxidative status of the testes through elevating TAC and ameliorating MDA and NO levels. More importantly, melatonin therapy suppressed BEP-evoked apoptosis by modulating Bcl-2, Bax, Caspase-3, p53, and TNF-α expression in testes.

Conclusions

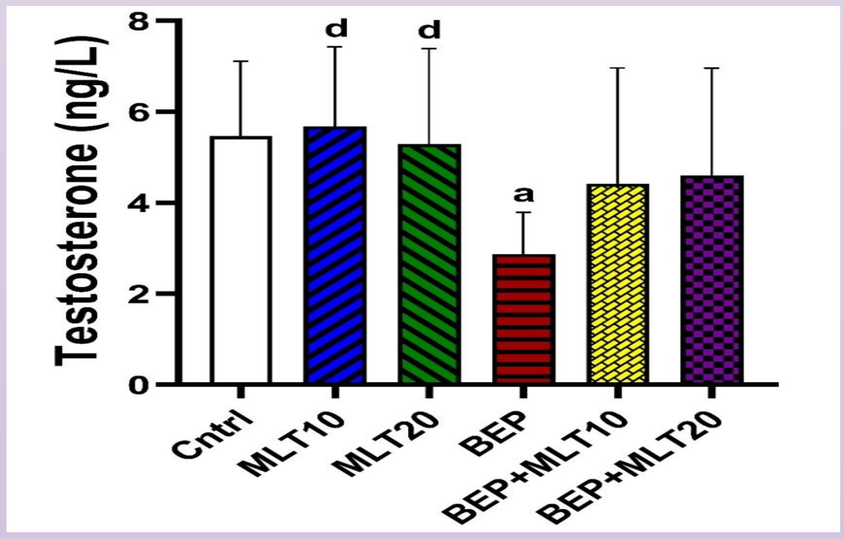
In conclusion, melatonin protects the testes against BEP-induced testicular damage by attenuating nitro-oxidative stress, apoptosis, and inflammation, which provides evidence for melatonin as a possible clinical therapy against BEP-associated gonadotoxicity and male sub/infertility.

Parameter	Cntrl	MLT 10	MLT 20	BEP	MLT10+BEP	MLT20+BEP
Testis Volume ( )	1079.20 ± 121.34	1124.42 ± 87.85^{d}	1127.9 ± 94.42^{d}	760.02 ± 164.47^{b}	849.68 ± 95.51^{a}	930.10 ± 77.79^{c}
Tubule Volume ( )	898.18 ± 107.49	925.34 ± 38.23^{d}	928.68 ± 94.04^{d}	592.96 ± 123.88^{b}	683.64 ± 108.82^{b}	720.88 ± 80.18^{ac}
Interstitial Tissue Volume ( )	216.44 ± 21.30	194.20 ± 14.621	194.52 ± 12.97	184.76 ±35.39^{a}	154.40 ± 34.42^{b}	173.64 ± 19.09^{a}
Epithelial Height (µm)	122.70 ± 4.31	125.20 ± 4.42^{d}	124.44 ± 7.05^{d}	87.78 ± 14.27^{b}	116.82 ± 8.05^{d}	118.62 ± 5.12^{d}
Tubule Diameter (µm)	325.94 ± 11.45	328.76 ± 9.31^{d}	328.24 ± 7.71^{d}	250.40 ± 27.96^{b}	290.24 ± 23.90^{ad}	304.10 ± 13.40^{d}
Tubule Length (m)	21.50 ± 2.49	22.40 ± 0.94^{d}	22.28 ± 1.24^{d}	17.26 ± 1.64^{b}	19.50 ± 1.71^{c}	19.98 ± 2.28^{c}
Sperm's Tail Length (µm)	30.8040 ± 1.27414	31.4740 ± 1.69658^{d}	30.1140 ± 2.00213^{d}	24.8140 ± 1.18688^{b}	27.4800 ± .84637^{bd}	28.2260 ± .67107^{ad}

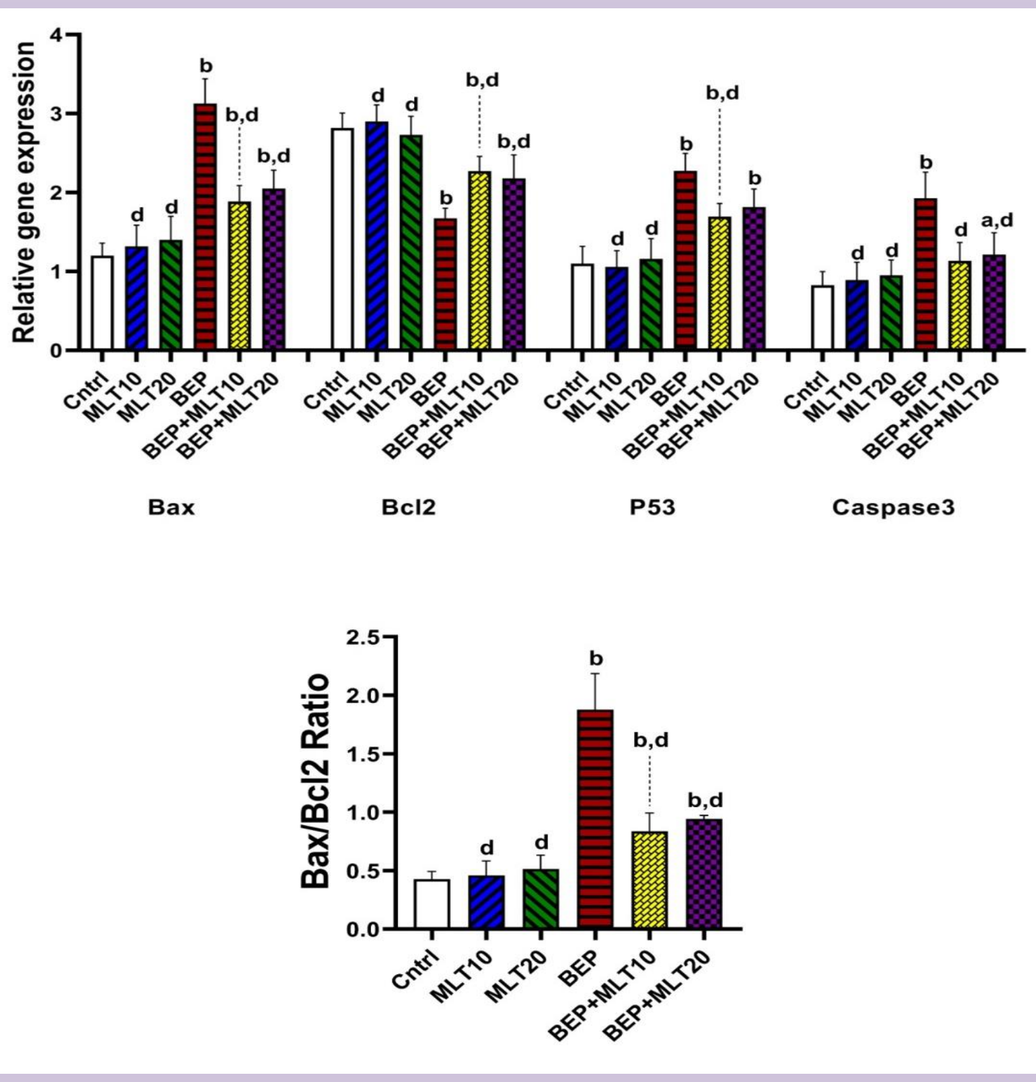
Total volume (mm^3) of the testis, seminiferous tubules, interstitial tissue, tubule diameter (µm)



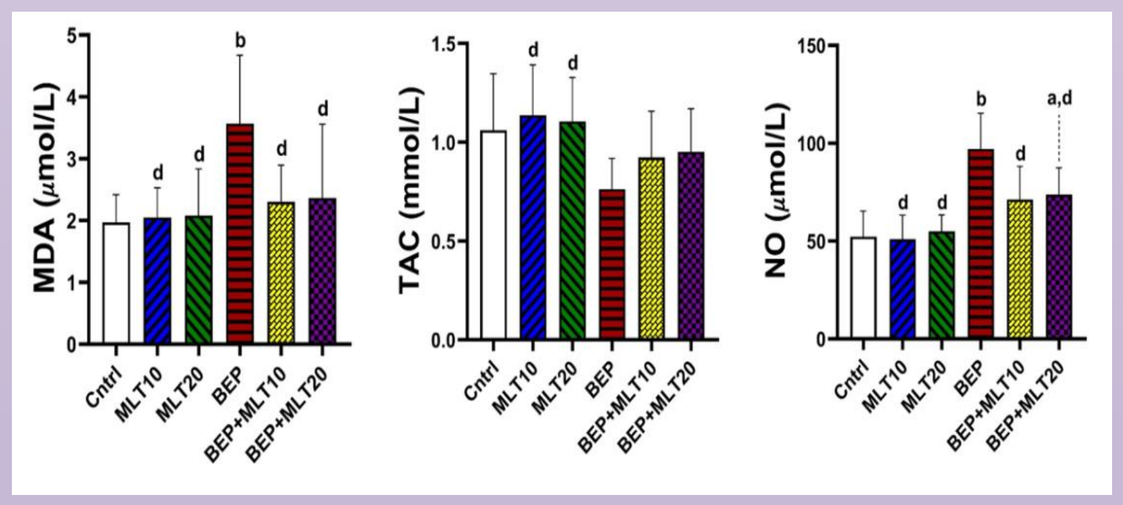
The effect of one cycle of BEP regimen with or without melatonin on sperm parameters



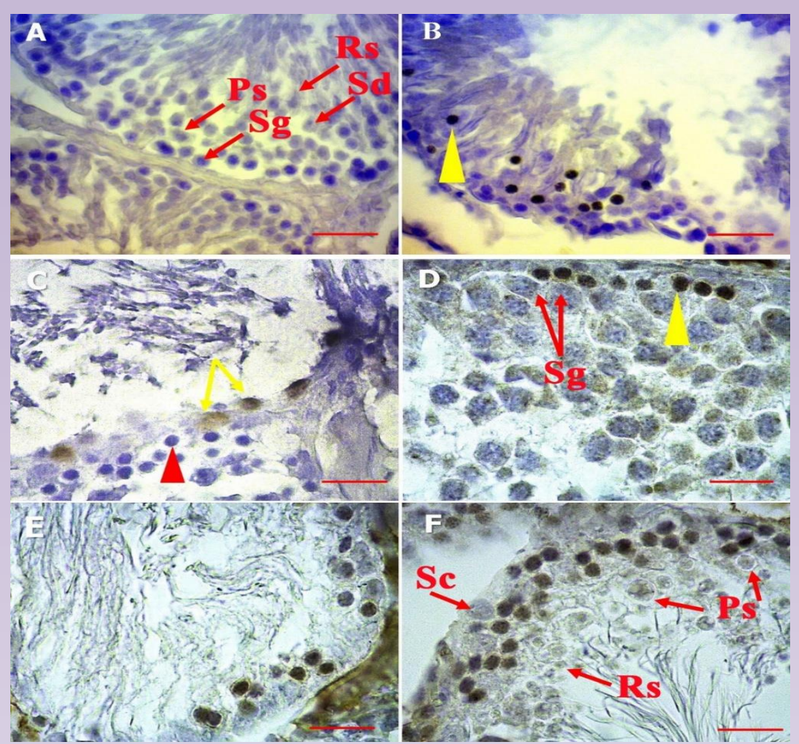
The effect of one cycle of BEP regimen with or without melatonine on testosterone level in the controls and experimental groups



The effect of one cycle of BEP regimen with or without melatonin on Bax, Bcl-2, Caspase-3 (C3), and p53 genes expression and also Bax/Bcl-2 ratio of testis



The effect of one cycle of BEP regimen with or without melatonin on testicular levels of malondialdehyde (MDA), nitric oxide (NO), and total antioxidant capacity (TAC)



The effect of one cycle of BEP regimen with and without melatonin on TNF-α, p53 and Bcl-2 expression in the testis.