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Research Article

Melatonin improves the Anti-HCC Effect of MSCs

Yasser Mohammed[1]*, Nabila I. El-Desouki[1], Mohamed A. Basyony[1], Walied S. Abdo[2], and Mohammed A. El-Magd[3]*

[1]*Department of Zoology, Tanta University, Egypt*
[2]*Department of Pathology, Kafrelsheikh University, Egypt*
[3]*Department of Anatomy, Kafrelsheikh University, Egypt*
[#]*Both authors contributed equally*

Abstract

This study was conducted to investigate the potential therapeutic effect of Melatonin (Mel) and/or mesenchymal stem cells (MSCs) on diethylnitrosamine (DEN)-induced rat model of HCC. Female mature rats were divided into 5 groups (n = 10/group): normal (Nor) group given saline orally for 20 weeks, and HCC group intraperitoneally injected with 200 mg/kg DEN, in addition to 3 treated groups; HCC + Mel (Mel) group given Mel intraperitoneally 20 mg/kg, twice a week, HCC + MSCs (MSCs) group intravenously injected by 1×10^6 cells/1 ml PBS, and HCC + MSCs (Mel +MSCs) group MSCs were pretreated with 5 μM Mel before injection. Rats injected in HCC group showed most deteriorated effect in form of increased mortality and relative liver weight, elevated serum levels of the liver damage enzymes, ALT, AST, and ALP, and the two cancer markers AFP and GGT in addition to increased pre-neoplastic nodules (altered hepatic foci) in liver tissues. Liver tissues of HCC group also exhibited lower level of apoptosis as indicated by decrease in DNA fragmentation, and downregulated expression of the apoptotic genes *p53* and *caspase 9*. Moreover, in this group the expression of inflammation-related genes (*IL6* and *TGFβ1*) was significantly upregulated. All these deleterious effects induced by DEN were reversed after administration of Mel and/ or MSCs with best improvement for the preconditioned group (MSCs+Mel). These findings reveal a better therapeutic effect for MSCs when preconditioned with Mel before injection and we attribute this beneficial effect, at least in part, to induction of apoptosis and inhibition of inflammation in HCC microenvironment. Therefore, pretreatment with Mel is recommended to enhance the therapeutic potential of MSCs for HCC.

***Corresponding authors**

Mohammed Abu El-Magd, Department of Anatomy, Faculty of Veterinary Medicine, Kafrelsheikh University, Egypt, Email: mohrizk73@yahoo.com

Yasser Mohammed, Department of Zoology, Faculty of Science, Tanta University, Tanta 31527, Egypt, Tel: 0000-0002-3314-9202; Email: harbya1981@yahoo.com

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a fatal disease that threatens the life of a large sector of population not only in the developing countries but also throughout the world. It comprises 85 - 90% of primary liver cancer cases, and is the third main cause of cancer death globally. Among the major HCC predisposing factors, infection by hepatitis C and B viruses comes on the top [1]. Failure of HCC treatment is mostly attributed to impairment of liver function, quick development of drug resistance, and presence of hepatic cancer stem cells [2]. In addition, hepatic cancer cells, similar to other cancer cells, keep their survival through inhibition of apoptosis and maintenance of inflammatory microenvironment [3]. Therefore, to kill cancer cells, these two mechanisms should be specifically targeted. Although, most anti-cancer drugs inhibit tumor growth through induction of apoptosis and reduction of inflammation, their uses usually accompanied by severe side effects due to lack of specific targeting. Thus, there is an urgent need to find suitable anti-cancer agents with highest efficacy and lowest adverse effects on normal (healthy) tissues.

Recently, mesenchymal stem cells (MSCs) were successfully used in cell-based therapy for several diseases, however, their potential therapeutic effects are often limited by inflammatory microenvironment of the hostile tissue [4,5]. Melatonin (Mel), an indoleamine secreted mainly by the pineal gland which has antioxidant and anti-inflammatory properties [6], was successfully used to enhance MSCs therapeutic effect against a large variety of diseased conditions [4-8]. The tumor suppressive effect of Mel was reported against different cancers and was attributed to its ability to induce apoptosis and prevent inflammation [9,10]. Based on the aforementioned data, we hypothesized that pretreatment of MSCs by Mel may improve their therapeutic outcomes (higher induction of apoptosis and inhibition of inflammation) against HCC. Therefore, this study was carried out to prove this hypothesis.

MATERIALS AND METHODS

MSCs culture and characterization

MSCs were isolated from the bone marrow of young male

rat long bones as previously described [11]. The isolated MSCs at passage 3 were characterized by positive expression for specific MSCs markers, CD105, CD90 and negative expression of CD45 (Becton, Dickinson) using flow cytometry (Attune, Applied Biosystem, USA).

Experimental design

The experimental protocol was approved by the Animal Ethics Committee of Kafrelsheikh University and was performed in accordance with the NIH guidelines on animal care. A total number of 50 healthy adult female rats with matched weights (140±5.25) and ages (6±0.12) weeks were housed in plastic cages (25-27°C and a 12 h light/dark cycle), fed a standard diet *ad libitum* with free access to water. The rats were distributed into 5 groups (n=10/group) as follow:

- Normal group (Nor): rats were orally administered saline throughout the experiment (20 weeks).

HCC group (HCC): normal rats were intraperitoneally injected once with diethylnitrosamine (DEN; 200 mg/kg in 1 ml of PBS, Sigma-Aldrich) and 1 week later, they were orally administrated 2-acetylaminofluorene (2-AAF; 150 mg/kg,Sigma Aldrich) for 2 weeks [12].

HCC+ Mel group (Mel): HCC rats were intraperitoneally injected by Mel (20 mg/kg, Sigma Aldrich) twice a week at week 9 and continued until week 14. The Mel dose and administration period was chosen based on a preliminary dose-time-response study (5, 10, 20, and 40 mg/kg).

HCC + MSCs group (MSCs): HCC rats were intravenously injected by a single dose MSCs (1×10^6 cells/1 ml PBS) at the beginning of week 12. The number and duration of MSCs was chosen based on a preliminary number-duration-response study.

HCC + MSCs preconditioned with Mel group (Mel+MSCs): MSCs were pretreated with 5 μM Mel for 24 hand then injected as previously mentioned in MSCs group.

Samples collection and preparation

Blood samples and serum preparation were done as previously described [13]. Following sacrificing by cervical dislocation under light anesthesia, the abdomen was incised and the liver was weighed and then thoroughly washed by saline. The liver was divided into two parts, the first part was quickly frozen in liquid nitrogen for RNA extraction and the second was preserved in 10% formalin for histological analysis.

Biochemical analysis

The serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), acid phosphatase (AP), α-fetoprotein (AFP), and γ-glutamyl transferase (GGT) were determined using commercial available kits and as previously described [14].

Detection of DNA damage by comet assay

The comet assay was performed on liver tissue as previously described [15]. The migration pattern of DNA fragments of 100 cells was evaluated with fluorescence microscope and Komet 5 image analysis software. The extent of DNA damage was assessed by the tail length, and the damage index which ranged from 0 [undamaged (tail length =0), 100 cells x 0] to 400 [maximal damage (tail length = 4), 100 cells x 4].

Histological analysis

Liver tissue samples were dehydrated in ethanol, cleared in xylene, impeded in paraffin to form tissue blocks, which then sectioned (4-5 μm), finally the slides were stained by hematoxylin and eosin (H&E).

Molecular analysis by qPCR

Total RNA was extracted from liver tissue using Gene JET RNA Purification Kit (Thermo Scientific) according to the manufacturer's instructions. Concentration and purity of the isolated total RNA was determined by nanodrop (Q5000, Quawell, USA) as previously described [13]. The cDNA was synthesized from RNA (5 μg) by reverse transcription using High-Capacity cDNA reverse transcription kit (Applied Biosystems). The produced cDNA was used as a template for real-time PCR reaction in the presence of QuantiTect SYBR Green qPCR Master Mix and gene specific primers designed by the Primer 3 web-based tool based on the published rat sequence (Table 1) along with Step One Plus real time PCR system (Applied Biosystem, USA) and reaction cycles as previously described [16]. The melting curves were constructed as previously described [17]. The differences in relative gene expression were normalized with β-actin expression and evaluated using $2^{-\Delta\Delta Ct}$ method. Levels were expressed relative to the normal control group.

Statistical analysis

One way ANOVA using GraphPad Prism 5 (GraphPad Software, Inc., LaJolla, CA, USA) was used to determine the difference between the groups. Comparison of means was carried out with Tukey's Honestly Significant Difference (Tukey's HSD) test. Data were presented as mean ± (SEM) and significance was declared at $P< 0.05$.

RESULTS AND DISCUSSION

In the present study, we hypothesized that MSCs pretreated with Mel before injection may improve HCC therapy probably through induction of apoptosis and inhibition of inflammation in HCC microenvironment. To prove our hypothesis, we first isolated MSCs from bone marrow of rats. Using phase contrast microscope, the isolated cells have an identical similarity with MSCs morphological features, including adhesiveness and fusiform (fibroblast-like) shape. This was further confirmed by flow cytometric analysis of the MSC surface markers CD105 and CD90 and the absence of the negative marker CD45 (data not shown).

MSCs pretreated with Mel decreased HCC progression and enhanced liver function

Herein, we monitored HCC progression by mortality rate, change in liver relative weight and serum levels of liver cancer markers (AFP and GGT). No mortality was recorded in all groups except HCC group, which showed a mortality rate of 20% (2/10). Expectedly, HCC group exhibited the highest relative liver weight when compared to the other groups (Figure1). In contrast, HCC

Table 1: Primers used for qPCR.

Gene	Forward primer	Reverse primer
p53	GTTCCGAGAGCTGAATGAGG	TTTTATGGCGGGACGTAGAC
Caspase9	AGCCAGATGCTGTCCCATAC	CAGGAGACAAAACCTGGGAA
IL6	TCCTACCCCAACTTCCAATGCTC	TTGGATGGTCTTGGTCCTTAGCC
TGFβ1	AAGAAGTCACCCGCGTGCTA	TGTGTGATGTCTTTGGTTTTGTCA
β-actin	AAGTCCCTCACCCTCCCAAAAG	AAGCAATGCTGTCACCTTCCC

rats treated with Mel and/or MSCs showed significant lower relative liver weight with lowest weight in Mel pretreated MSCs group, while no significant difference was observed among the Mel, and MSCs groups. As changes in mortality rate and relative liver weight are not enough to guarantee low carcinogenicity, we further estimated the serum levels of liver cancer markers (AFP and GGT) and notably found an association between this increase and AFP and GGT elevated serum levels in the HCC group. Again, AFP and GGT were significantly decreased by Mel and/or MSC treatment with the best improvement in the Mel + MSCs group (Figure 1). The effect of Mel and/or MSCs treatment on HCC was monitored by detection of fluctuations in serum levels of liver damage enzymes (ALT, AST, and ALP). As expected, HCC group exhibited higher serum levels of these enzymes, indicating liver dysfunction [18]. However, treatment with Mel and/or MSC decreased this elevated levels to levels comparable to that of normal control group, with best effect to the combined pretreated group (Figure 1). Collectively, these findings indicate that pretreatment of MSCs with Mel gives better therapeutic effect against HCC than each alone. Similar results were reported in rat model of HCC induced by CCL_4 [19], liver injury [20], and chronic liver disease [21].

MSCs pretreated with Mel restored the distorted liver histology in HCC

Unlike in normal group (Figure 2A), rat liver in HCC group had pre-neoplastic nodules with altered hepatic foci (AHF) that characterized by presence of a large number of hexagonal, vacuolated cells and oval cells (Figure 2B). These AHF were decreased after treatment with Mel and/or MSCs with a notable apoptosis (marked by a condensed nucleus and a clear eosinophilic cytoplasm) in MEL+MSCs group (Figure 2C-E). In agreement, Mel has been shown to decrease DEN-induced HCC [22], and ovarian cancer [23] in rats. Similar AHF were also observed in HCC rat model induced by other carcinogens [24]. These distorted liver histological architecture observed in HCC group plays an integral role in elevation of liver enzymes in blood. Damage of tissues, especially cell membrane, lead to release of these enzymes from the cells to circulation [14].

MSCs pretreated with Mel induced apoptosis in HCC

Previous studies have reported anti-cancer effect for Mel, at least in part, through induction of apoptosis in cancer cells [9,10]. In this study, we evaluated this apoptotic effect by assessing DNA fragmentation (by comet assay), and changes in expression of apoptotic genes, p53 and caspase 9, (by qPCR). DNA damage was significantly increased after administration of Mel and MSCs alone or in combination with preconditioning, as revealed by a high damage index compared with that in the HCC group (Figure 3). Again, the highest DNA damage was noticed in animals given both Mel and MSCs with preconditioning. However, no significant difference in DNA damage was noticed between the Mel group and the MSCs group. In agreement, administration of Mel induced higher DNA fragmentation (higher TUNEL-positive cells) in ovarian cancer [23]. It also inhibits progression of HCC both *in vitro* [9] and *in vivo* [22], via apoptosis.

To check the involved molecular apoptotic mechanism of Mel and/or MSCs, changes in the expression of the proapoptotic genes, *p53* and *caspase 9*, were studied. Livers of HCC rats exhibited a significant downregulation in *p53*, and *caspase 9* relative to normal control rats (Figure 3). This reduced expression was significantly increased following treatment with Mel and/or MSCs, with highest expression in Mel+MSCs group. Overall, these results suggest that Mel and MSCs can induce apoptosis in HCC, with best results obtained when MSCs pretreated with Mel. In consistent with our results, Mel was reported to induce expression of *p53*, and caspases genes and proteins in several cancer cell lines and livers of HCC rats [9,22]. In contrast to its apoptotic effect on cancer cells, Melhas anti-apoptotic effect on healthy cells and induces their proliferation [25], suggesting a differential influence on cell viability according to the type of target cells.

MSCs pretreated with Mel reduced inflammation in HCC

Another possible way, by which cancer cells maintain their high proliferative capacity and survival, is the production of pro-inflammatory cytokines. Therefore, inhibition of inflammation is an urgent need for killing cancer cells. Mel can alleviate acute and chronic liver diseases by targeting inflammatory cytokines [20]. To check whether Mel and/or MSCs have anti-inflammatory effect on HCC, expression of the inflammation-related genes (*IL6* and *TGFβ1*) was determined in rat livers from all the groups. The HCC group exhibited the highest expression of *IL6* and *TGFβ1*as compared to other groups. In contrast, treatment by Mel and/or MSCs significantly decreased this elevated expression, with the best improvement in the Mel + MSCs group (Figure 4). In consistence, Mortezaee et al. [19], also showed downregulated expression of *TGFβ1*gene in liver of CCL_4-induced HCC rats following treatment by MSCs preconditioned by Mel. *TGFβ1* is the most important cytokine in the pathogenesis of liver fibrosis which precedes HCC [22].

The important questions why the best effect was noticed when MSCs pretreated with Mel before administration. It is possible that Mel can directly activate MSCs proliferation. In

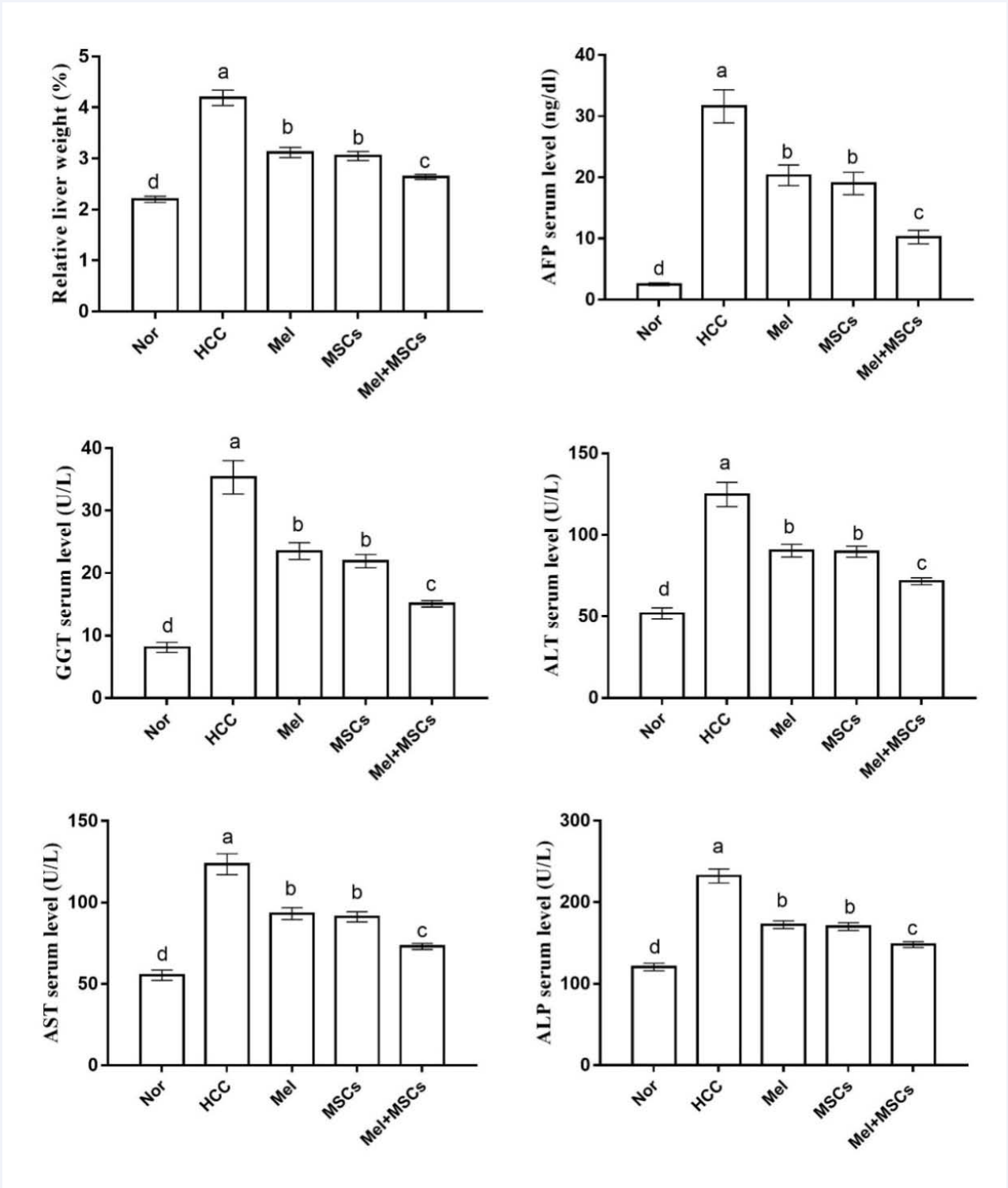

Figure 1 Effect of Mel and/or MSCs on relative liver weight and serum levels of liver cancer markers and liver enzymes (AST, ALT, ALP).Normal control (Nor), HCC, HCC treated by Mel (Mel), HCC treated by MSCs (MSCs), and HCC treated by Mel and MSCs (Mel + MSCs) rats. Values are expressed as mean ± SEM (n= 7). Values carrying different lower case letter are significantly different at P<0.05.

support to this notion, previous studies have shown that Mel can bind to its receptors (MT1 and MT2) in MSCs and subsequently triggers their survival and migration [26,27]. In addition, Mel can regulate stem cell proliferation [26,27], motility [28], and differentiation into hepatocyte-like cells [21]. Another possible mechanism is the ability of Mel to improve the hostile hepatic tissue for MSCs homing and proliferation. The hostile hepatic microenvironment in HCC (high inflammation and hypoxia)

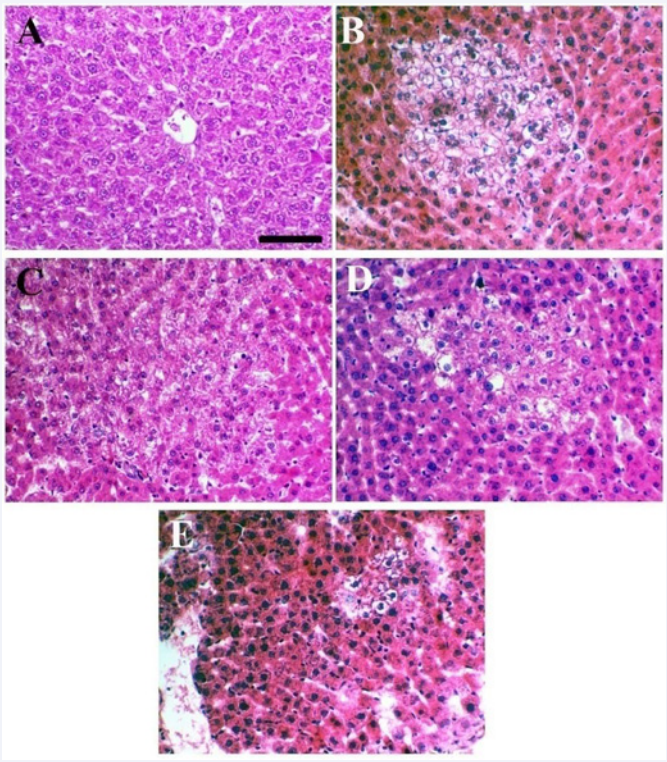

Figure 2 Photomicrographs of liver sections stained by H&E in normal (A),HCC(B),Mel (C),MSCs (D),and Mel + MSCS (E) groups. Scale bar = 50 µm.

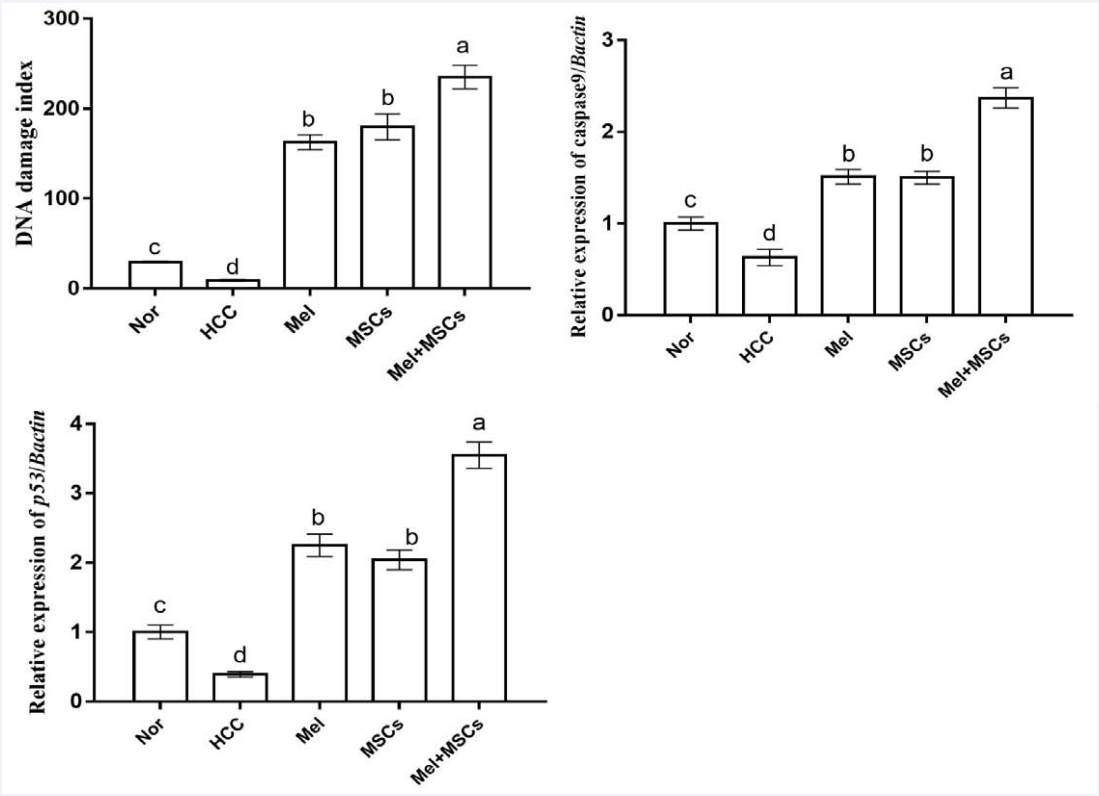

Figure 3 Effect of Mel and/or MSCs on DNA fragmentation as determined by comet assay and on expression of apoptoticgenes, *p53* and *caspase 9*, in livers of HCC rats as detected by qPCR. Data presented as fold change from the normal (Nor) controlgroup. Values are expressed as mean ± SEM (n= 7).Values carrying different lower case letters are significantly different at P<0.05.

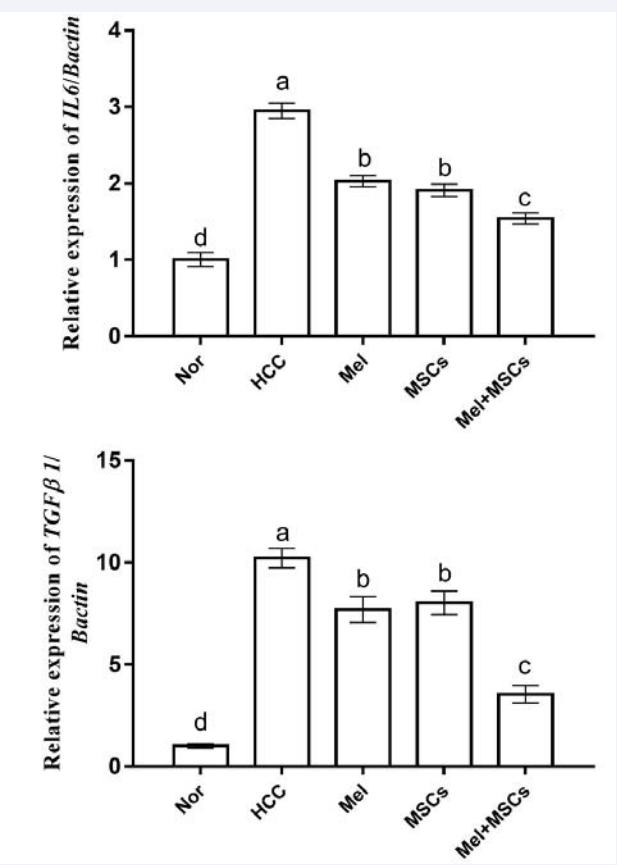

Figure 4 Effect of Mel and/or MSCs on DNA fragmentation as determined by comet assay and on expression of inflammation-related genes, *IL6*, *TGFβ1*, in livers of HCC rats as detected by qPCR. Data presented as fold change from the normal (Nor) controlgroup. Values are expressed as mean ± SEM (n= 7).Values carrying different lower case letters are significantly different at P<0.05.

induces apoptosis in MSCs thereby, restricting their therapeutic potential [29]. Mel is well known for its anti-inflammatory effect and so when given with MSCs, it will decrease the inflammation and so maintain MSCs viability. For this reason, most of recent studies used combined Mel and MSCs therapy, for example in the treatment of liver fibrosis [19,21] ischemic injuries of the heart [7], brain [5], lung [8], kidney [30], and bowel [4]. Application of this treatment strategy may also need fewer MSCs for homing, and so this will decrease MSCs accumulation in other organs.

CONCLUSION

The present study reported that pretreatment of MSCs with Mel before transplantation enhances the anti-HCC effect of MSCs through induction of apoptosis and inhibition of inflammation. The results of this study may be valuable in treatments targeting liver diseases in patients. However, further molecular investigations (especially on micro RNAs, and long non coding RNAs) are required to give more details on how Mel pretreatment maximizes the therapeutic potential of MSCs.

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