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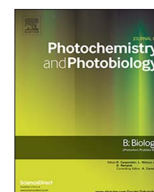

Nigella sativa oil modulates the therapeutic efficacy of mesenchymal stem cells against liver injury in irradiated rats

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ABSTRACT

Stem cell transplantation is a novel strategy for regenerative medicine in liver disease. This study was conducted to explore the modulatory effect of *Nigella sativa* oil (NSO) on the therapeutic potential of mesenchymal stem cells (MSCs) against irradiation-induced liver damage in rats. Liver damage was induced by a total body exposure to a single dose of 7 Gy. NSO (2 mg/kg/day) was then given orally for 4 consecutive weeks starting 24 h after irradiation with or without a single intravenous MSCs administration, then rats were sacrificed four weeks after exposure to γ radiation. Data revealed that irradiation elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities in serum, increased hepatic malondialdehyde (MDA) content and reduced hepatic superoxide dismutase (SOD) activity. Furthermore, it caused elevation in pro-inflammatory mediators such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) associated with reduction in anti-inflammatory cytokine interleukin-10 (IL-10) and it increased fibrogenic marker transforming growth factor-β (TGF-β) in liver tissues. It was observed that combined NSO/MSCs therapy provided more beneficial tissue repair comparable to MSCs alone as demonstrated by modulating the tested parameters. Finally, these results were confirmed by histopathological examination. In conclusion, dual therapy with NSO and MSCs could serve as a promising approach for alleviating radiation-induced liver injury in patients with radiotherapy.

1. Introduction

Exposure to radiation is commonly used during radiotherapy, medical diagnosis, dental radiography and several imaging protocols as well as accidental radiation releases. However, gamma irradiation generates reactive oxygen species (ROS) that initiates a state of oxidative stress and promotes an inflammatory response and consequently contributes to multiple organ dysfunctions. Interestingly, liver is a radiosensitive organ that is more susceptible to radiation damage. Hepatic radiotherapy for liver cancers leads to radiation-induced liver damage which could be a life threatening factor [1]. The current therapies for the damage prompted by radiation relies on anti-oxidative and anti-inflammatory potentials of different drugs and their ability to inactivate ROS.

New therapeutic strategies such as stem cell transplantation has gained considerable interest as a promising approach for regenerative medicine in liver disease. Trials of stem cell treatment in patients with liver disease have already started but are still at a very preliminary stage [2]. Indeed, mesenchymal stem cells (MSCs) were initially isolated from bone marrow (BM), so it is not surprisingly that bone marrow derived mesenchymal stem cells (BM-MSCs) have been the golden standard in MSCs experiments. MSCs are non-haematopoietic, multipotent cells that show low immunogenicity, low probability of being tumorigenic after transplantation into patients or animals, and presented no ethical problems [3]. In addition, MSCs are able to differentiate into osteoblasts, adipocytes, and chondrocytes. MSCs has also the tendency to migrate to damaged tissue sites, owing to their chemotactic abilities [4].

Through the release of different growth factors and cytokines, MSCs can exert immnomodulatory, anti-inflammatory, pro-angiogenic, and anti-apoptotic effects as well as restoring hepatocyte number and supporting regeneration and self-renewing of resident stem cells, thereby augmenting liver function and counteracting progressive liver fibrosis [5]. BM-MSCs have established to impact tissue regeneration and demonstrated efficacy in radiation protection. Recent reports illuminated the therapeutic efficacy of MSCs in alleviating irradiation-induced intestinal injury in mice via elevating the intestinal growth factors and anti-inflammatory cytokines and enhancing intestinal stem cells proliferation that facilitated epithelial mucosal regeneration [6]. Moreover, the beneficial effects of MSCs have been confirmed in a liver

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fibrosis rat model as it suppressed fibrosis progression and slightly ameliorated liver function [7].

Nevertheless, there are still many limitations for stem cell therapy such as poor survival of engrafted stem cells [8]. Recently, several studies have examined the effects of simultaneous use of MSCs with pharmacological agent on liver repair. The target of pharmacotherapy could be the improvement of survival, mobilization, recruitment, proliferation and differentiation of transplanted cells. This strategy was confirmed in a previous experimental study where combining melatonin therapy with stem cells promoted MSCs differentiation into hepatocytes by certain signaling pathways [9]. Likewise, melatonin abolished free radicals to improve cell viability and enhanced osteogenic differentiation to improve bone remodeling in experimental periodontitis model in rats [10].

Nigella sativa L. oil (NSO) is a herbaceous plant belonging to the Ranunculaceae family. It exhibits a wide variety of medicinal properties such as antioxidant, anti-inflammatory, hepatoprotective, nephroprotective, antihyperlipidemic, antibacterial as well as antitumour activity [11–12]. According to literature, NSO activities are mainly attributed to its constituents of thymoquinone (TQ) [13]. It has been reported that NSO has shown promising results in several models such as hepatic ischemia reperfusion [14], cardiotoxicity [15], rheumatoid arthritis [16] and colitis [17]. NSO has been effectively used in children with acute lymphoblastic leukemia as it reduces hepatotoxicity induced by methotrexate [18]. Furthermore, earlier studies demonstrated that NSO treatment could significantly preserve hepatocytes from injury [19].

Accordingly, the current study was designed to explore the modulatory effect of NSO on the therapeutic efficiency of BM-MSCs in treatment of irradiation-induced liver damage in rats.

2. Materials and Methods

2.1. Animals

Adult male albino rats (150–180 g) were supplied from the animal breeding unit of the Nile Company for Drugs (Cairo, Egypt). Animals were adapted for one week before starting the experiments under appropriate conditions of temperature, humidity and light. They were fed standard rodent chow diet and allowed free access to water ad libitum. The study was performed in accordance with the ethical standards for animal experimentation at the National Center for Radiation Research and Technology (NCRRT), Cairo, Egypt.

2.2. Chemicals

The NSO was obtained from Imtenan, herbal drugstore (Cairo, Egypt), Dulbecco's modified Eagle's medium (DMEM) and fetal bovine serum were supplemented from GIBCO/BRL, Life Technologies, USA. All other chemicals used in this study were of analytical grade and were purchased from Sigma-Aldrich Chemical Company (St. Louis, Missouri, USA).

2.3. Irradiation Process

Whole body γ irradiation of rats was performed at the National Center for Radiation Research and Technology (NCRRT) using a Gamma cell-40 supplied with a Caesium-137 irradiation source. Rats were exposed to a single dose level of 7 Gy delivered at a dose rate of 0.44 Gy/min.

2.4. BM-MSCs Isolation, Expansion and Labeling

For isolating BM-MSCs as previously described [20], rats (150–180 g) were euthanized with thiopental overdose, bone marrow was collected by flushing the femurs and tibiae with DMEM complete culture media supplemented with 10% fetal bovine serum. The isolated nucleated cells were centrifugated and resuspended in complete culture media containing 1% penicillin–streptomycin. Cells were incubated at 37 °C in 5% humidified CO_2 for 12–14 days till formation of large colonies. When the culture flask was 80% confluent, cultures were washed twice with phosphate buffer saline (PBS) and the adherent cells were trypsinized with 0.25% trypsin in 1 mM EDTA for 45 min at 37 °C. The resulting cultures were mentioned as first-passage cultures.

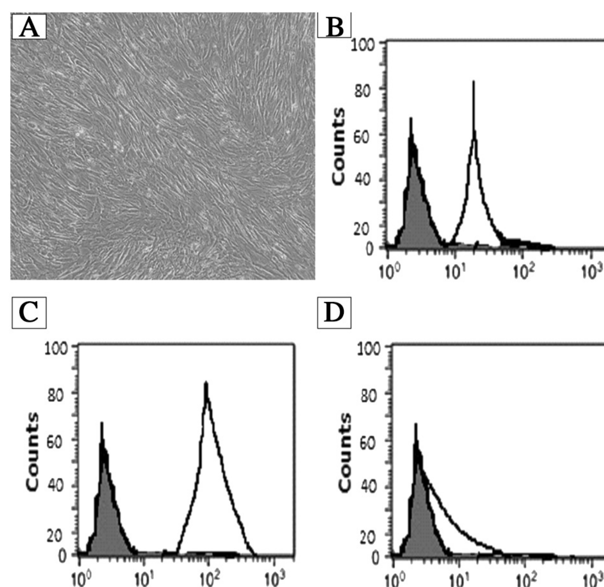

Fig. 1. Characterization of bone-marrow derived mesenchymal cells. (A) Spindle-shaped MSCs population in culture. (B–D) Flow cytometric immunophenotyping analysis for identification and characterization of BM-MSCs (CD29 +, CD90 + and CD34 −, respectively).

Characterization of BM-MSCs in culture was tested by its morphology that exhibited a typical MSCs phenotype with fibroblast-like spindle shape (Fig. 1A). In addition, immunophenotypes of mesenchymal cell surface markers were examined by flow cytometric analysis to identify the expression of CD29 +, CD90 + and CD34 − in MSCs (Fig. 1B–D). Collected MSCs during the 4th passage were labeled with red fluorochrome PKH26 (Sigma-Aldrich Co., USA). It seems that labeled cells maintain biological and proliferating activities and are applied for cell tracking [21]. In the present study, the harvested cells were mixed with PKH26 reagent then the mixture was incubated for 2–5 min at 25 °C. Blocking of staining action was done by adding the same volume of serum and incubated for 1 min then centrifuged for 10 min. The supernatant was removed and washed three times. Finally, complete culture medium was applied, and cells were centrifuged and were observed under a fluorescent microscope to detect and trace the cells [22].

2.5. Experimental Design

Rats were allocated into five groups (n = 8); group I received saline and served as normal control, group II was exposed to a single dose of 7 Gy and served as irradiated control group, groups III was whole body γ irradiated then received NSO at a dose of 2 mg/kg/day [23] orally by gastric intubation for 4 consecutive weeks starting 24 h after irradiation, group IV received a single intravenous injection of 10^6 BM-MSCs 24 h after irradiation, while, group V received combined therapy of NSO as in group III 2 h prior to administration of BM-MSCs as in group IV. Twenty-four hours following the last dose of NSO, animals were anesthetized with urethane (1.2 g/kg, i.p.), blood samples were withdrawn from the retro-orbital venous plexus using non heparinized capillary tubes then animals were sacrificed and liver samples were

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