



e-ISSN: 2319-8753 | p-ISSN: 2347-6710

# IJIRSET

International Journal of Innovative Research in  
**SCIENCE | ENGINEERING | TECHNOLOGY**



# INTERNATIONAL JOURNAL OF INNOVATIVE RESEARCH

IN SCIENCE | ENGINEERING | TECHNOLOGY

Volume 11, Issue 2, February 2022

**ISSN** INTERNATIONAL  
STANDARD  
SERIAL  
NUMBER  
INDIA

Impact Factor: 7.569

# Improving Nitrite Salt Toxicity (as Food Additive) to Pulmonary Tissue by Bone Marrow-Derived - Mesenchymal Stem Cells on Rats Model

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**ABSTRACT:** The study aimed to conduct the toxicological effect by Sod. nitrite on the lungs of adult male Wistar rats. Also, to examine the possible therapeutic effect of the MSCs against Sod nitrite. The adult rats were divided into 5 groups (n=12 in each group) as follows, Two groups are received distilled water and served as a control content of two groups (one for 2 weeks and the other for 3 weeks) to be compared with the treated groups. NT2 group was daily administered Sod. nitrite subcutaneous injection at a dose of (35 mg/kg b.wt/ day) for 2 weeks. NT3 group treated with the same dose for 3 weeks. NT2-S group was received Sod. nitrite for 2 weeks, then injected with MSCs ( $2 \times 10^6$  cells intravenously, once). NT3-S group was treated with Sod. nitrite for 3 weeks, and then injected with MSCs. The scarification was done after 4 weeks of MSCs treatment. After that, they were sacrificed. The levels of oxidative stress (NO, MDA and DNA F %) were significantly increased, while (CAT and TAA) were significantly reduced in all treated groups in comparison with the control. The use of MSCs for therapy induced a significant improvement for the Lung of the biochemical investigated parameters but not to the level of the control, the histological investigations support these results. The finding suggests that one marrow-derived-MSCs associated with the administration of nitrite led to improved biochemical markers, concluded that is the therapeutic effect of stem cells are treatment obvious alveolus-like spaces lined by flat or cubical pneumocytes on the surface of a thin layer of vascular connective tissue resembling an alveolar wall. A few macrophages are present within the alveolar. Also, showed hyaline membrane disease in the lung bronchioles in the pink membranes are partly fibrin exudates and partly necrotic squamous epithelial cell hyperplasia.

**KEYWORDS:** Food Additive, Nitrite, Pulmonary, Mesenchymal Stem Cells, Rats.

## I. INTRODUCTION

Food Additive is any substance added to food, not normally used as a typical ingredient of the food and not normally consumed as a food by itself, they may be natural or synthetic. Therefore, the modern food-industry dependence on processing and additives increases and has continually produced new chemicals to control, preserve, and transform our food [1]. Therefore, they are classified into various categories such as antimicrobial agents, antioxidants, artificial colours, artificial flavours and flavour enhancers, chelating agents and thickening and stabilizing agents [1,2]. Common food additives endorsed by Food and drug Organization "FDA" are utilized to preserve taste and colour as sodium nitrite [3]. The food additives are fundamental for nourishment capacity whereas, they can provide rise to certain unfavourable wellbeing issues as well as cause diverse sensitivities and hyperactivity within a few individuals who are touchy to particular chemicals [4]. The food containing added substances can cause asthma and dermatitis [5].

Hypoxia is generated when residing in high altitude environments or when receiving a mixture of polluting gases. Thus, this condition is also a factor in various pathological processes of the lung, acute lung injury, asthma attacks, atelectasis, COPD and idiopathic pulmonary hypertension. [6], edema [7, 8], and pneumonitis [9, 10]. Chronic hypoxia is associated with vascular proliferation [11], increased vascular reactivity [12], and chronic pulmonary hypertension [13-14]. Various lung diseases have identified the involvement of reactive oxygen species (ROS) in pathogenesis [15].

Nitrite is a multifunctional additive that is commonly used in the meat industry. However, due to the negative effect of nitrite on human health, it is important to reduce the amount of nitrite added to meat products. Plant extracts appear to be a suitable alternative for synthetic nitrite. In general, plant extracts show antioxidant and antimicrobial



activities, can prevent the discolouration of meat products, and, in proper quantities, do not hamper the flavour of the product [16]. The toxic effects of nitrates and nitrites are well documented in mammals including impairment of reproductive function [17]. Sodium nitrite is a powerful oxidizing agent that causes hypotension and limits oxygen transport and delivery in the body through the formation of methemoglobin. Clinical manifestations can include cyanosis, hypoxia, altered consciousness, dysrhythmias, and death. The majority of reports on sodium nitrite poisonings have been the result of unintentional exposures. Sodium nitrite exerts its effect by the generation of free radicals that impair oxidant / antioxidant balance [18]. In such concern, the role of antioxidants in the reduction of sodium nitrites toxicity is well established [19]. Sodium nitrite induces chemical hypoxia through reducing the oxygen-carrying capacity of the blood by converting haemoglobin to methaemoglobin leading to hemic hypoxia [20]. It helps in the production of free radicals, leading to increased lipid peroxidation, which plays a vital role in posing toxic effects in different body organs [21]. Scientific evidence illustrated the health hazards of exposure to nitrites for a prolonged time. Nitrites affected several body organs due to oxidative, inflammatory and apoptosis properties [22].

The fatal level of sodium nitrite is within the range of 22 to 23 milligrams per kilogram of body weight. Lower dosages of sodium nitrite have caused intense methemoglobinemia, especially in newborn children, coming about from the change of nitrate to nitrite after consumption [23].

The production of ROS (reactive oxygen species) by mammalian mitochondria is important because it underlies oxidative damage in many pathologies and contributes to retrograde redox signalling from the organelle to the cytosol and nucleus [24]. Nitric oxide can function as an intracellular messenger, an autacoid, a paracrine substance, a neurotransmitter, or as a hormone that can be carried to distant sites for effects. Thus, it is a unique simple molecule with an array of signalling functions [25]. Nitrite related nitrogen species such as nitric oxide (NO) are a matter of increasing scientific controversy. An increase in the content of reactive nitrogen species may result in nitrosative stress—a deleterious process, which can be an important mediator of damage to cell structures, including lipids, membranes, proteins and DNA [26].

Mesenchymal stem cells (MSCs) are multipotent cells derived from adult tissues [27]. MSCs secrete multiple molecules, including anti-inflammatory cytokines, growth factors, and anti-microbial peptides, and appear as fine-tuners of host inflammation [27]. Adult mesenchymal stem cells (MSCs) are considered highly promising candidate cells for regenerative applications because they possess a high proliferative capacity and the potential to differentiate into other cell types [28]. MSCs are also actively investigated for clinical use as gene delivery agents to enhance tissue regeneration, destroy cancer cells, and regenerate cartilage and bone [29]. It has been suggested that the high plasticity of adult MSCs, which makes them an attractive candidate for cell-based therapies, is the result of low-level expression of a variety of gene families that characterize differentiated progeny, endowing them with a state of readiness to differentiate along one direction or another, depending on external cues [30]. MSCs are hypothesized to persist in the adult for tissue repair and remodelling, among other functions, in perivascular niches throughout the body [31]. Previous studies showed that MSCs administration in animal models of acute lung injury increased the ability of the host to eliminate the agent, regulate neutrophil recruitment, and reverse altered lung permeability, without additional injury [32–33]. Also, the intraperitoneal (i.p.) route for the administration of MSCs was recently described [34].

The work in this paper is divided into two stages. 1) The primary aim was to conduct histological studies by sodium nitrite as a food additive on the lungs of adult male rats. 2) Investigate the biochemical of treated sodium nitrite NO, MDA, DNA F%, CAT and TAA markers. 3) Therapeutic potentials of Bone marrow-derived - mesenchymal stem cells.

## II. METHODOLOGY

### Materials And Methods

**Animals Experimental model:** Seventy-two male Wistars were aged 4 months ( $200 \pm 10$  g) were obtained from the Animal House of the National Medical Research Center in the city of Tripoli, Libya. The rats were raised in plastic cages, with 8 rats in each cage measuring 50 X 60 X 30 cm, in a 12 - hour dark/light environment at  $25 \pm 2$  ° C. A commercial pelleted diet was used during the experiment. The rats were acclimatized to the laboratory environment for one week before the beginning of the experiment. The experimental protocols and procedures were in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines.



Doses and injections; Sod. Nitrite was purchased in crystalline form from the Nur Al-Elmia Company. It was dissolving in distilled water at 27°C and given subcutaneously into the backs of the rats at a dose of 35 mg/kg of body weight/day according to [35] daily.

**Isolation of MSCs from rats:** Bone marrow cells were collected from six rats and cultured according to a previously described procedure [36]. These cells were known as MSCs according to their morphology, adherence, and their ability to differentiate into osteocytes [37], and chondrocytes [38]. PKH26, a red fluorochrome, was used to label the undifferentiated MSCs while maintaining their biological and proliferating potential [39] as stated by the manufacturer's reference (Sigma, Saint Louis, Missouri, USA). Cells were intravenously injected into the tail vein of rats. One month later, the homing of injected MSCs in the brain tissue, i.e., PKH26 - stained cells, was detected by a fluorescence microscope (LABOMED LX400 SERIES, USA). Inflammation-directed MSC homing involved numerous vital cell trafficking-related molecules such as chemokines, matrix metalloproteinases, and adhesion molecules [39].

**Experimental design:** The animals were randomly divided into 5 groups, with 12 rats in each group. - C (group 1): Dorsal subcutaneous injection of distilled water\_ 0.1 mL / 100 g body weight \_ for 2, and 3 weeks as control groups, followed by sacrifice by decapitation. NT2 (group 2): Subcutaneous injection of Sod. nitrite (35 mg / kg / d) for 2 weeks; Sigma St. Louis, MO, USA, as a pure white powder (assay 299 %) (Bhanumathy et al., 2010) for 14 days. NT3 (group 3): Subcutaneous injection of Sod nitrite for 3 weeks. NT2-S (group 4): Subcutaneous injection of Sod. nitrite for 2 weeks. NT3-S (group 5): Subcutaneous injection of Sod. nitrite for 3 weeks, followed by one intravenous injection for 28 days. injection of MSCs via the tail vein (2 x 10<sup>6</sup> cells/rat). After the experiment, rats that received the last dose, 24 hours later, were sacrificed by rapid decapitation. The total time for the experiment was 7 weeks (Fig 1).

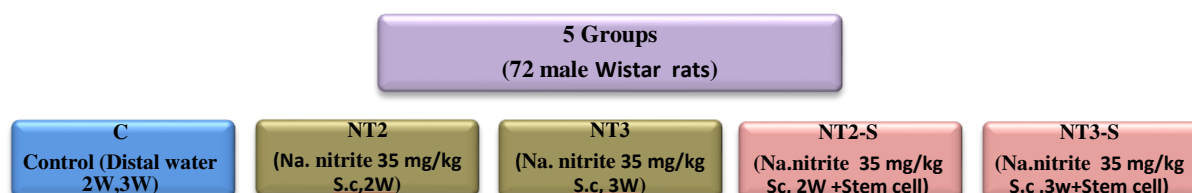


Fig 1: Graphic diagram for the experimental

**Statistic Analysis:** Data Were Statistical Analyzed Using SPSS Software, Chicago, IL, USA and other SET. One-Way Analysis of Variance Was Used for Comparison differences among groups. Data were expressed as Mean \_ Standard Deviation (SD). Duncan multiple range tests was used for Post Hoc analyses, and  $p < 0.05$  was accepted as significant.

**Oxidative stress evaluation:** The lung sample was weighted and immediately excised on jacket ice, every part was homogenized in 10 mMole/L phosphate buffer saline (10% W/V) of PH 7.4, and centrifuged. The supernatant was used for estimation of Nitric oxide contents, Malondialdehyde contents, DNA fragmentation percentage, Catalase, Activity and Total antioxidant activity.

**Microscopical Studies:** The part of the lung for pathological studies were immediately excised at the time of sacrifice as fast as possible and cut into small pieces with a sharp razor while being immersed into the appropriate fixatives. Specimens for light microscopically preparations were cut in dimensions of about 1/2x1/2x1/2 centimetres.

**Histopathological Evaluation:** From each rat lungs were carefully dissected and fixed in Bouin's solution for routine histological analysis. Following fixation and embedded in paraffin wax at 60°C. Serial transverse sections were then cut at 5-6 microns in thickness using Cambridge Rocking Microtome and affixed to slides. For the general histological examination, sections were stained in Hematoxyline and Eosin (H&E) then washed, dehydrated, cleared, and mounted with canadapalsam for permanent preparations[40].

### III. EXPERIMENTAL RESULTS

#### Biochemical investigation:

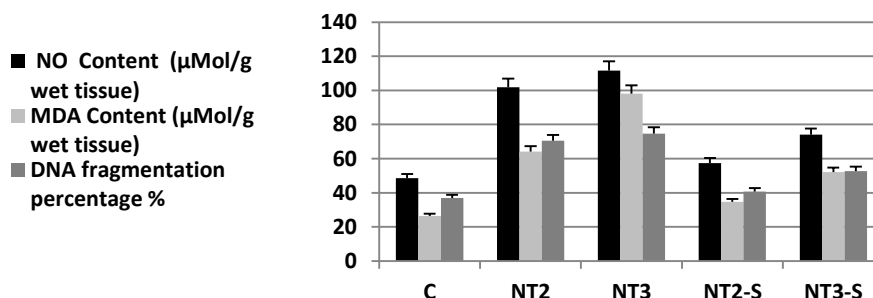
- 1) Assessment of oxidative stress markers nitric oxide (NO) content, Malondialdehyde (MDA) content and DNA fragmentation percentage (DNA F %), in different experimental groups was illustrated in table (1) and Fig (1). The data revealed a significant increase in all treated groups compared to the control groups. While, the oxidative

markers of NO, MDA and DNA were decreased significantly in NT2-S and NT3-S treated groups in comparison with the NT treated rats. There was a significant increase in NO, MDA and DNA content of NT3-S as compared to the NT2-S group.

Table(1) : Mean values of nitric oxide content (NO) (mMole/g wet tissue), malondialdhyd content (MDA) ( $\mu$ Mole/g wet tissue), DNA fragmentation percentage (DNA F %), catalase activity CAT ( $\mu$ /g wet tissue) and lung total antioxidant activity TAA (mMole/g wet tissue) in various treated groups.

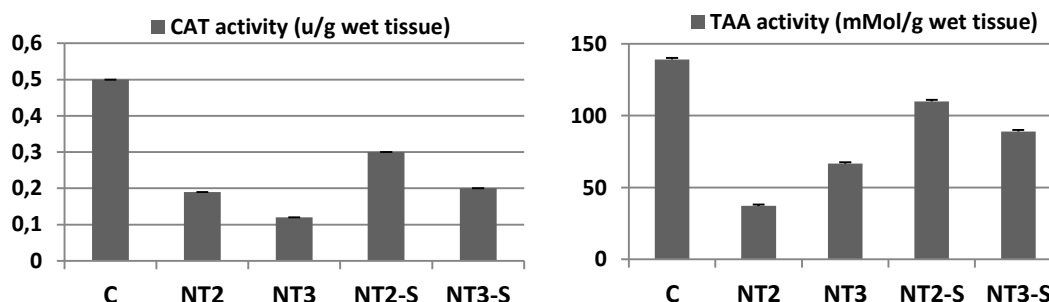
Groups Parameter	C	NT2	NT3	NT2-S	NT3-S
NO	48.50 $\pm$ 0.634	101.91 $\pm$ 1.490 <sup>a</sup>	111.52 $\pm$ 1.601 <sup>a</sup>	57.47 $\pm$ 0.692 <sup>abc</sup>	74.03 $\pm$ 1.631 <sup>abcd</sup>
MDA	26.62 $\pm$ 0.545	64.18 $\pm$ 0.644 <sup>a</sup>	98.02 $\pm$ 2.498 <sup>ab</sup>	34.68 $\pm$ 0.985 <sup>abc</sup>	52.11 $\pm$ 1.74 <sup>abcd</sup>
DNA	36.90 $\pm$ 0.575	70.44 $\pm$ 1.142 <sup>a</sup>	74.59 $\pm$ 0.264 <sup>a</sup>	40.66 $\pm$ 0.281 <sup>abc</sup>	52.26 $\pm$ 1.112 <sup>abc</sup>
CAT	0.50 $\pm$ 0.011	0.19 $\pm$ 0.003 <sup>a</sup>	0.12 $\pm$ 0.005 <sup>ab</sup>	0.30 $\pm$ 0.006 <sup>abc</sup>	0.20 $\pm$ 0.010 <sup>abc</sup>
TAA	139.1 $\pm$ 4.302	37.18 $\pm$ 2.063 <sup>a</sup>	66.60 $\pm$ 1.007 <sup>ab</sup>	109.9 $\pm$ 4.706 <sup>abc</sup>	88.91 $\pm$ 1.977 <sup>abcd</sup>

Values are means of 8 rats  $\pm$  S.E at ( $p < 0.05$ ). (a) significant change from control group (C group), (b) significant change from treated group with Sod. nitrite for 3 weeks (NT2 group), (c) significant change from treated group with Sod. nitrite for 3 weeks (NT3 group), (d) significant change from the treated group by Sod. nitrite for 2 weeks + MSCs (NT-2S group) and (e) significant change from the treated group by Sod. nitrite for 3 weeks + MSCs (NT-3S group).



**Fig2:** Total and differential Malondialdehyde (MDA) content and DNA fragmentation percentage of different treated groups (mean value  $\pm$  S.E).

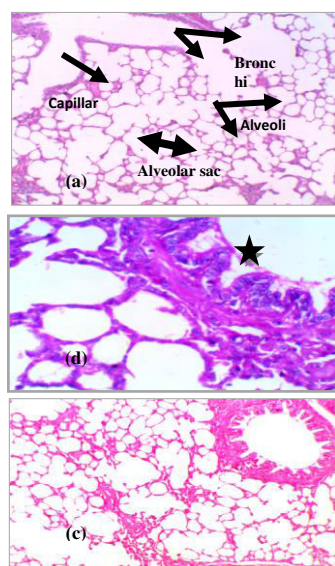
- 2) Assessment of Antioxidant markers catalase activity (CAT) and total antioxidant (TAA) activity, The data presented in table (1) and Fig (3) indicates the lung catalase activity (CAT) and total antioxidant (TAA) activity. A significant decrease was shown in all treated groups in comparison with the control group. In addition, the lung CAT activity and TAA) activity of NT2-S and NT3-S groups were significantly increased in comparison with the NT2 and NT3 groups. On other hand, The CAT activity and total antioxidant (TAA) activity of the NT3-S group was decreased significantly when compared with the NT2-S.



**Fig 3 :** Total and differential Catalase activity (CAT) and Total Antioxidant Activity (TAA) of different treated groups (mean value  $\pm$  S.E).

**Histological investigation:**

Histological examination of the normal lung section exhibited terminal bronchioles, respiratory bronchioles, alveolar sacs and ducts, the respiratory bronchioles lead to the alveolar ducts which are lined with a single layer of cubical cells the alveolar ducts leads to a blind alveolar sac which is formed of numerous pulmonary alveoli. the latter are thin-walled polyhedral formations that are separated by a closely meshed network of fine elastic and reticular fibres (Fig4. a) the alveolar wall includes 3 types of cells namely, the lining epithelial, endothelial cells of capillaries and connective tissue cells (Fig4. b-c), This section through the lung shows the structures of the respiratory zone. The respiratory bronchiole, lined with simple cuboidal epithelium, has alveoli out pocketing from its wall. Alveolar ducts lead to alveolar sacs, terminal clusters of alveoli. Simple squamous epithelium forms the alveolar walls. The most striking histological feature recorded in rats of Na-nitrite administered for 2 weeks induced Inflammation around bronchi and bronchioles is common hyaline material in lung alveoli walls and fibrosis, and alveolar septa, the collapse of alveolar with loss normal architecture, congestion of blood vessel and thickening their walls could be seen (Fig5. a, b). Also, Fibrosis thickened wall of lung alveoli filled with granular necrotic debris and minimal fatty degeneration were evident (Fig5. C, d). Exposure of rats to Na-nitrite dramatically affected the normal pattern of the lung tissue showing acute lung injury with hyaline material the interstitium space around throughout alveolar wall (Fig5. e).

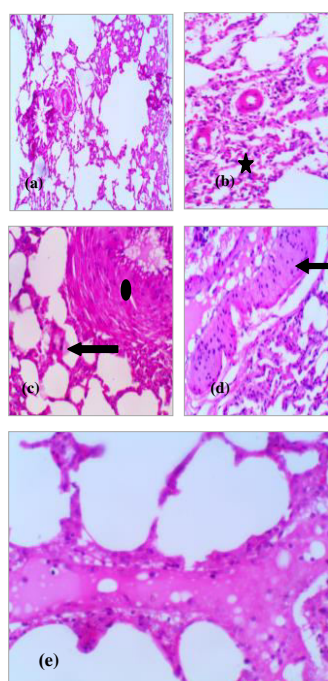


**Fig 4: Photomicrograph of normal lung tissue:**

(a) (C group) showing, normal capillary, alveolar sacs and bronchi (H&E X 200).

(b) Magnification of normal bronchiole illustrating the respiratory epithelial cell lining the bronchiole cavity and mucus secretion (star) (H&E X 400).

(c) Normal bronchiole illustrates the respiratory epithelial cells and alveolar sacs cavity (H&E X 200).



**Fig 4: Photomicrograph of Lung section with Na. nitrite:**

(a) (NT2 group) rats showing Necrotic epithelium, fibrosis in blood capillary (H&E X 200).

(b) Massive hemorrhage accompanied by scanty inflammation (star) (H&E X 200).

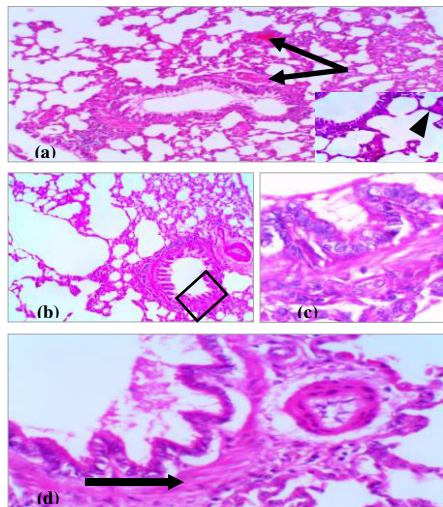
(c) hyaline material in lung alveoli (arrow) and fibrosis and thick walled arteries (H&E X 400).

(d) (NT3 group) rats showing fibrosis thickened wall of lung alveoli filled with granular necrotic debris and minimal fatty degeneration (H&E X 200).

(e) (NT3 group) rat showing acute lung injury with hyaline material interfered by fatty vacuoles, rupture and necrotic change the alveolar wall (H&E X 400).

These sections of the lung from rats whose treated with MSCs after injection with Na-nitrite for 2 weeks NT2-S group is showing significant improvement with mild thickening congestion and expansion of pulmonary alveolar walls, with numerous pulmonary blood capillary blocked by blood (Fig6. a). Furthermore, the lung section showed hyaline membrane disease in the lung bronchiole in the pink membranes are partly fibrin exudates and partly necrotic squamous epithelial cell hyperplasia, (Fig6. b, c). Notice prominent infiltrate with neutrophils and lymphocytes, bronchiole basement membrane separated from its epithelial cells and localized thickening of the intima of pulmonary arteriole with a detachment of outer layer (Fig6. d). Histological exclamation of the lung section of rat injection with Na-nitrite for 3 weeks and MSCs treated showing adenomatous hyperplasia showing localized centriacinar alveolar wall thickening and increased numbers of alveolar lining cells, irregular twisting collapsed alveolar, and fibrosis of pulmonary arteriole (Fig7. a). Haemorrhage, aggregation of Invasive inflammatory lymphocytes and the lymphoid cells infiltrating the bronchiolar epithelium forming lymph epithelial lesions were noticed (Fig7. b). Moreover, Lung tissue manifested alveolar lined by flat pneumocytes type I and cubical pneumocytes type II on the surface of a thin layer resembling an alveolar wall. A few macrophages are present within the alveolar (Fig7. c).





**Fig 6: Lung section from stem cell treatment rats**

(a)(NT2-S group) showing increased thickening pulmonary alveolar walls, Alveolar wall congestion and expansion, numerous pulmonary blood capillary blocked by blood (arrows) (H&E X 200) and magnified area (H&E X 400).

(b and magnification c)(NT2-S group) showing hyaline membrane disease in the lung bronchiole in the pink membranes are partly fibrin exudates and partly necrotic squamous epithelium cell hyperplasia (H&E X 200) and (H&E X 1000).

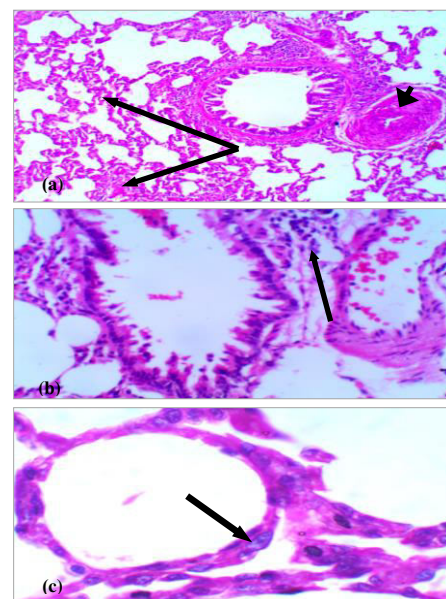
(d)(NT2-S group) showing Prominent infiltrate with neutrophils and lymphocytes (arrow), bronchiole basement membrane separated from its epithelial cells, and localized thickening of intima of pulmonary arteriole with detachment of outer layer (H&E X 400)

**Fig 6: Lung section from stem cell treatment rats:**

(a) (NT3-S group) showing adenomatous hyperplasia showing localized centriacinar alveolar wall thickening and increased numbers of alveolar lining cells (arrows), Irregular twisting collapsed alveolar, fibrosis of pulmonary arteriole wall (head) (H&E X 200).

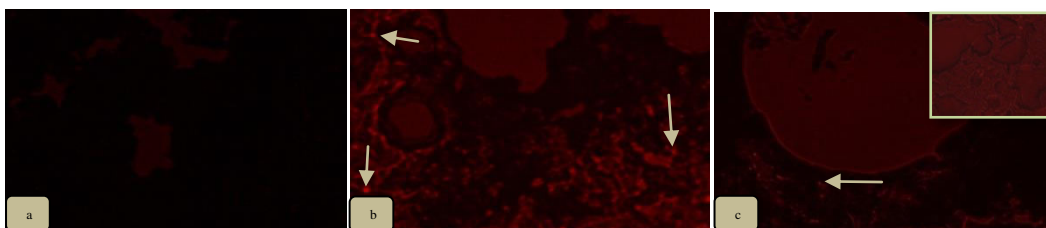
(b) (NT3-S group) showing hemorrhage, and aggregation of Invasive inflammatory lymphocytes (arrow). The lymphoid cells infiltrate the bronchiolar epithelium forming lymphoepithelial lesions (H&E X 400).

(c) (NT3-S group) illustrates that alveolus-like spaces lined by flat or cubical pneumocytes on the surface of a thin layer of vascular connective tissue resembling an alveolar wall. A few macrophages are present within the alveolar (arrow) (H&E X 1000)



### Homing efficiency

The lung tissue of control rats was without cells homed (Fig7. a). In the pulmonary tissue which more sensitive tissue in the body, there are numerous labelled MSCs with PKH26 fluorescent dye was detected in the tissue sections in administered Sod. nitrite for 2 weeks in the NT2-S group that is obviously clear in the (Fig7. b). Rats were treated with Sod. nitrite for 3 weeks in the NT3-S group, less fluorescent dye was homed the lung tissue than in the prior group (Fig7. c).



**Fig 7: Representative fluorescence micrographs of pulmonary tissues which were treated by Na-nitrite following MSCs injection showing the homing of MSCs by PKH26 dye.**



(a) C group showing absence of MSCs labelled by PKH26 dye. (b) NT2-S group showing PKH26 fluorescent dye detected in the lung tissues confirming that these cells homed into the lung. (c) NT3-S group MSCs were detected in the pulmonary tissues, confirming that these cells homed into the lung., but they were less compared with NT2-S group.

Figures show the results of text detection from an image and inpainting by using an exemplar-based Inpainting algorithm. Fig (a) shows the original image, (b,c) is the image obtained by applying the first set of criteria.

#### IV. DISCUSSION

In the present study, The treatment with food additives as Sod nitrite by (35 mg/kg sc) NT groups rats appeared hyaline material in lung alveoli and fibrosis, and thick-walled arteries. Also, showing Fibrosis thickened wall of lung alveoli. In support of this result, stereological and confocal microscopy studies demonstrated that chronic hypoxia increased wall thickness but did not alter the luminal diameter of intra-acinar vessels, suggesting that smooth muscle hypertrophy occurred in an outward direction without luminal encroachment [41,42]. Moreover, increases in total pulmonary vessel length, volume, endothelial surface area, and endothelial cell numbers suggested that chronic hypoxia caused pulmonary angiogenesis, raising the possibility that total cross-sectional area of the pulmonary vasculature was preserved, as suggested by an early morphological study[43]. In this case, the increased muscularity of small pulmonary arteries could increase vasomotor responses without increasing basal PVR, thereby explaining the rapid, nearly complete elimination of chronic hypoxic pulmonary hypertension by Rho-kinase inhibitors [44,45]. Chronic hypoxic exposure, which accompanies lung diseases such as chronic obstructive pulmonary disease and pulmonary arterial hypertension, results in sustained HPV and vascular remodelling, which in turn leads to acceleration of right ventricular failure [46]. Therefore, the resolution of HPV is a viable strategy for the treatment of these patients. Nitric oxide is a potent endothelial-derived vasodilating agent [47]. Inhaled administration of exogenous NO has a vasodilatory effect that is selective for the pulmonary vasculature [48]. In the present study, treatment with food additives such as Sod nitrite by (35 mg/kg Sc) the oxidative markers of NO, MDA and DNA revealed a significant increase in all treated groups compared to the control groups. These come about are in agreement with [3] shows an increment in ALT, AST and MDA in Sod nitrite treated rats. Receptive nitrogen species created by the introduction to nitrite is considered one of the foremost critical causes of carcinogenesis through its response with body tissues and activating lipid peroxidation, DNA injuries, chemical inactivation and harm of diverse organs [49]. The oxidative stress pointer is lipid peroxidation which might be credited to the oxidative cytotoxicity of nitrite [50, 51, 52,53]. The treatment with food additives such as Sod nitrite by (35 mg/kg Sc) NT groups rats showed necrotic epithelium and fibrosis in blood capillary and exhibited massive haemorrhage accompanied by scanty inflammation. Our result agreement with [54] reported that Hypoxia can cause capillary recruitment and de-recruitment and may also change vascular permeability. Furthermore, pulmonary arteries and veins may be more permeable per unit surface area than capillaries [55,56]. Thus determining the effects of hypoxia on lung fluid filtration is an imprecise way to identify the vessels responsible for HPV.[6] The isolated lung studies confirmed not only the pulmonary pressor response to sod. nitrite was caused by vasoconstriction, since the lungs were perfused at constant flow and outflow pressure, but also that HPV did not depend on neural or humoral influences from outside the lung. These studies validated the insight of [57] that hypoxia could act through local mechanisms to cause pulmonary vasoconstriction and thereby regulate local ventilation-perfusion relationships. Peripheral vessels dilate in response to low oxygen, whereas the vessels of the pulmonary vasculature constrict to shunt blood away from the poorly ventilated region, thereby matching ventilation to perfusion. Hypoxic pulmonary vasoconstriction is a fast response that occurs in pulmonary arteries and veins but is greatest in small resistance arteries. It is intrinsic to pulmonary vasculature smooth muscle cells and is initiated by inhibition of one or several  $K^+$  channels which set the membrane potential. The resulting depolarization activates voltage-gated  $Ca^{2+}$  channels, which raises the cytosolic calcium level and causes myocyte constriction. While  $K^+$  channels are the effectors of hypoxic pulmonary vasoconstriction, it is not clear whether they are intrinsically  $O_2$ -sensitive or under the control of a "real"  $O_2$  sensor. Recent work from [58] proposes that mitochondria, through the production of oxygen reactive species, could modulate the activity of the channel. Indeed, certain  $K_v$  channels are rich in cysteines and respond to the local redox environment, tending to open when oxidized and close when reduced. Hypoxia is a potent stimulus for the release of a variety of factors by pulmonary vascular endothelium that both serves to recruit fibrocytes as well as induce phenotypic conversion to fibroblasts or myofibroblast. Notably, depletion of circulating fibrocytes abrogated hypoxia-induced perivascular remodelling in rats [59]. Circulating fibroblasts may also be important in lung cancer development or metastasis [60]. The development of inflammation in response to hypoxia is clinically relevant. Ischemia in organ grafts increases the risk of inflammation and graft failure or rejection [61]. Moreover, increases in pulmonary cytokine levels were shown to correlate with greater ischemic injury of transplanted lungs and loss of graft function[62,63]. In the setting of obesity, an imbalance between the supply of and demand for oxygen in enlarged adipocytes causes tissue hypoxia and an increase in inflammatory adipokines in





fat. The resultant infiltration by macrophages and chronic low-grade systemic inflammation promotes insulin resistance [64]. Taken together, these clinical studies indicate that hypoxia promotes inflammation [65]. Our results are in favour of such suggestion.

The histochemical study suggests that the development of MSCs after long-term (induced by chronic exposure to sodium nitrite) caused middle to improve. Following intravenous infusion of MSC populations expanded in vitro, despite the large number that becomes trapped in the lungs, some MSCs subsequently do home to damaged tissue, such as infarcted myocardium, traumatic brain injury, fibrotic liver and chemically damaged lungs, and to various types of tumours [66]. Our histopathological results are in agreement with observation [67] reported that pulmonary respiratory functions significantly improved for up to 18 days of hypoxia-preconditioned MSC treatment. Expression of inflammatory factors and fibrotic factor were all downregulated in the lung tissues of the hypoxia-preconditioned MSC-treated mice. Histopathologic examination observed a significant amelioration of the lung fibrosis. Furthermore, [67] idiopathic pulmonary fibrosis is a progressive diffuse parenchymal lung disorder of unknown aetiology. Mesenchymal stem cell (MSC)-based therapy is a novel approach with great therapeutic potential for the treatment of lung diseases. MSCs relatively improve the histopathological changes induced in the testis of rats. This protection is multifactorial, including modulating the oxidative stress reaction, tissue damage and repair. In this respect, [68] have reported that pretreatment with MSCs attenuates lipopolysaccharide-induced acute lung injury in rats through inhibition of neutrophilic recruitment, inflammation, oxidative stress and apoptosis. One theory of tissue repair holds that organ injury is 'sensed' by stem cells that migrate to the site of damage and differentiate into organ-specific cells, promoting structural and functional repair [68, 69]. Hypoxia, characteristic of many lung injuries and diseases, can also alter MSC expression of cell surface molecules and secretion of soluble mediators by MSCs [70, 71]. Overall, this illustrates a rapidly growing body of evidence demonstrating that MSCs are malleable and can be significantly influenced by local inflammatory environments, including those found in lung injuries. Although the mechanisms of the MSC effects are not completely understood [72], soluble mediators released by the MSCs appear to play important roles in the amelioration of acute and fibrotic injuries in the different models. Similar results were obtained Mesenchymal stem cell (MSC)-based cell therapy is a potential therapeutic approach for the treatment of various lung diseases [73].

## V. CONCLUSION

This study showed that Sodium nitrite administered at different time intervals have impaired antioxidant enzyme, caused inflammation around bronchi and bronchioles is common hyaline material in lung alveoli and fibrosis, and the risk of alveolar and thick-walled arteries and Fibrosis thickened wall of lung alveoli filled with granular necrotic debris and minimal fatty degeneration compared with controls, and MSCs therapy improved these findings. This suggests that MSCs alleviated lung injury induced by sodium nitrite. Nitrite obvious alveolus-like spaces lined by flat or cubical pneumocytes on the surface of a thin layer of vascular connective tissue resembling an alveolar wall. A few macrophages are present within the alveolar. Also, showed hyaline membrane disease in the lung bronchioles in the pink membranes are partly fibrin exudates and partly necrotic squamous epithelial cell hyperplasia. However, The longer period of receiving nitrite as a food additive caused the greater the damage by its toxicity and the lower the possibility of treating side effects. So, The utilization of food additives added substances must be diminished to avoid health damage. future studies are required. Additionally, an in vitro study should be required to confirm the differentiation of stem cells.

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