

*Original Research Article*

# Bis4-(4'-hydroxy-3'-methoxy benzylidene aminophenyl) telluride prevents sodium nitrite induced changes in haematological parameters of adult's male rats

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## Abstracts

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Sodium nitrite ( $\text{NaNO}_2$ ) is highly toxic, flammable and a strong oxidant substance. It oxidizes hemoglobin into methemoglobin. The aim from this study is to evaluate the role of the novel organotellurium compound [bis4-(4'-hydroxy-3'-methoxy benzylidene amino phenyl) telluride] in preventing sodium nitrite induced hematological changes in adult's male rats. Forty adults' male rats were used in this study; they were divided into 5 equal groups. The 1<sup>st</sup> group is control, the 2nd group was given 0.2%  $\text{NaNO}_2$  in the drinking water, the 3<sup>rd</sup> and 4<sup>th</sup> groups were given the novel compound orally in dose of 11 and 5.5mg/kg, respectively as well as  $\text{NaNO}_2$ , and the 5<sup>th</sup> group was given the novel compound only (11mg/kg). Analysis of haematological parameters was carried out at the end of the experimental period (one month).  $\text{NaNO}_2$  intoxication causes decreases in hemoglobin concentration, haematocrit ratio, erythrocytes and platelets number and increases leukocytes. While no alteration in MCV, MCH, and MCHC was noticed. Changes in the haematological parameters are ameliorated by the administration of the novel organotellurium compound. The ability of the novel organotellurium compound in ameliorating sodium nitrite induced haematological changes may be attributed to its antioxidant and free radicals scavenging activity.

**Keywords:** Novel organotellurium compound, Sodium nitrite, Hemoglobin

## INTRODUCTION

Sodium nitrite is highly toxic, flammable and a strong oxidant chemical substance. About 5% daily nitrite intakes come from cured meats. The toxic effects of nitrites in mammals include gonadotoxicity, hepatotoxicity, neurotoxicity, and carcinogenicity (Aoyagi et al., 1980; Krishnamoorthy et al., 2008; Premanand and Ganesh, 2010; Hassan et al., 2010; Pavlova et al., 2013; Sherif and Al-Gayyar, 2013). Moreover, nitrite oxidizes hemoglobin leading to the formation of methaemoglobin and consequently tissue hypoxia (Shumilova et al., 2006), it also disturbs the function of endocrine glands especially the adrenal cortex and the thyroid gland by

interference with their hormone synthesis (Til et al., 1997; Kostogryns et al., 2006).

Nitrite oxidizes hemoglobin (Hb) into methemoglobin (met-Hb) causing methemoglobinemia (Shumilova et al., 2006), in severe form it leads to tissue hypoxia (Hunter et al., 2011). The oxidized hemoglobin is reduced mainly by methemoglobin reductase enzyme, the deficiency of this enzyme in children results in congenital methemoglobinemia (Jabłońska-Skwiecińska et al., 1989). It has been found that when rats exposed frequently to sodium nitrite, they become adapted to its oxidizing effect. In these rats, the nitrite induced changes in hemoglobin are

disappeared gradually and methemoglobin reductase level increased in erythrocytes (Pankow et al., 1975).

A highly significant reduction in erythrocytes and leukocytes counts, Hb concentration and Hematocrit ratio (Hct) has been observed in immature growing male albino rats orally administered sodium nitrite (30mg/kg daily) for 6 months, whereas mean cell volume (MCV) and mean cell hemoglobin (MCH) were significantly increased (Helal et al., 2008). Similar changes in erythrocytes and leukocytes count, Hb concentration and Hct ratio has been observed in rats administered lower doses of NaNO<sub>2</sub> (10mg/kg) (Helal and Elsaid, 2006). A Significant reduction in erythrocytes count, Hb concentration and Hct ratio was reported in male rats injected with NaNO<sub>2</sub> by intraperitoneally (10 mg/kg, i.p.), whereas no effect was observed on MCV, MCH and MCHC (Rahman et al., 2009). On the other hand, Gluhchevaa et al. (2012) mentioned a reduction in erythrocyte count and increase in MCH and MCHC after injection of higher dose of NaNO<sub>2</sub> (50 mg/kg, i.p.). In pregnant rats, both Hb concentration and Hct ratio were reduced after sodium nitrite intake (Mowafy et al., 2001). Hemolytic anemia, reticulocytosis, methemoglobinemia and leukocytosis were reported in rats acutely intoxicated with sodium nitrite (Miasoedova and Nazarov, 2003). It has been observed that arginine and glutamate are capable of ameliorating the significant increase in differential leucocytes percentage in male rats given 0.2% NaNO<sub>2</sub> in the diet for 6 weeks (El-Sheikh and Khalil, 2011). Ivanova and Nazarova (2004) reported three-phase changes in erythrocytes count, Hb concentration and activation of erythropoiesis and erythrophagocytosis after chronic nitrite intoxication in rats, these changes are reversed by administration of alpha-tocopherol. Methylene blue treatment also capable of reversing nitrite induced hematological changes in rats (Yasmin et al., 2008). In rabbits, nitrites and nitrates pollution causes reduction in erythrocytes count and leucocytes count and Hb concentration (Mahboob et al., 2021). Therefore, the aim from this study is to evaluate the role of the novel organotellurium compound [bis(4-(4-hydroxy-3-methoxybenzylidene amino phenyl) telluride)] in preventing sodium nitrite induced hematological changes in adult's male rats.

## MATERIALS AND METHOD

### Chemicals

Sodium nitrite (NaNO<sub>2</sub>) solution is freshly prepared and given in a dose of 0.2% (2 g/L) in the drinking water (Nyakas et al., 1990; Krishnan et al., 2011). The novel organo-tellurium compound (R<sub>2</sub>Te), bis [4-(4-hydroxy-3-methoxybenzylidene-aminophenyl)] telluride, was given orally by gavage as suspension in 0.2 ml of corn oil in a

dose of 5.5 and 11mg/kg which is corresponding to 1/20 and 1/40 of its LD50, respectively (Shalaby et al., 2010; Ibrahim et al., 2012).

### Experimental animals

Forty adults' male rats (*Rattus norvegicus*) of 5 months age and weighting 300 ± 25g were used in this experiment. Rats were kept under standard environmental conditions at temperature 24-28°C and 12 hours dark/light period. They are housed in polyethylene cages with wire mesh, 2rats per cage. They fed standard rat pellets and fresh clean water was provided at libitum. The rats were acclimatized for two weeks before the start of the experiment.

### Experimental design

The rats were divided randomly into 5 equal groups (8 rats in each group) and treated for one month as following:

- 1) Control group: In which rats were given corn oil
- 2) NaNO<sub>2</sub> group: In which rats were given corn oil and NaNO<sub>2</sub>.
- 3) R<sub>2</sub>Te (11mg/kg) and NaNO<sub>2</sub> group: In which rats were given R<sub>2</sub>Te (11mg/kg B.W) and NaNO<sub>2</sub>.
- 4) R<sub>2</sub>Te (5.5mg/kg) and NaNO<sub>2</sub> group: In which rats were given R<sub>2</sub>Te (5.5 mg/kg B.W) and 0.2% NaNO<sub>2</sub>.
- 5) R<sub>2</sub>Te group: In which rats were given 11mg/kg of R<sub>2</sub>Te (11mg/kg B.W.).

At the end of the experiment (one month), the rats were sacrificed after light chloroform anesthesia. Blood sample was obtained by 10 ml disposable syringe of 22G needle from posterior vena cava, as it enters the right ventricle (Parasuraman et al., 2010). Blood was transferred into EDTA tube for hematological investigations. Automated hematology (BC-5300, Mindry, China) was used for measurement of erythrocyte, leukocytes, differential leukocytes and platelet counts; Hb concentration, Hct ratio, MCV, MCH and MCHC.

### Statistical method

Computerized SPSS (Statistical Package for Social Sciences) (V.13) program was used for analysis of results. The data were tabulated as mean ± standard deviation (mean ±SD) and computerized SPSS (Statistical Package for Social Sciences) (V.13) program were used for their analysis. One way analysis of variance (ANOVA), Post-hoc LSD procedure was used to test the difference between the mean of the groups; P ≤ 0.05 was considered statistically significant (SPSS, 2001).

**Table 1.** Effects of NaNO<sub>2</sub> and R<sub>2</sub>Te on Hb concentration Hct ratio, erythrocytes and platelets count (mean ± SD, n=8)

Group	Hb (g/dL)	Hct (%)	Erythrocytes ×10 <sup>6</sup> /μL	Platelets ×10 <sup>3</sup> /μL
Control	12.42 ± 0.99 a	0.431 ± 0.023 ab	7.55 ± 0.23 b	941.5 ± 33.6 ab
NaNO <sub>2</sub> (0.2%)	10.82 ± 0.69 b	0.380 ± 0.221 c	6.83 ± 0.42 c	839 ± 12.0 c
R <sub>2</sub> Te (11mg/kg) and NaNO <sub>2</sub> (0.2%)	12.73 ± 0.88 a	0.422 ± 0.025 b	7.33 ± 0.55 b	933.5 ± 21.3 b
R <sub>2</sub> Te (5.5mg/kg) and NaNO <sub>2</sub> (0.2%)	12.85 ± 0.50 a	0.451 ± 0.021 a	7.94 ± 0.49 ab	932.3 ± 17.1 b
R <sub>2</sub> Te (11mg/kg)	12.55 ± 0.72 a	0.428 ± 0.008 ab	7.49 ± 0.31 b	958.3 ± 25.0 a
LSD	1.6	0.024	0.45	24.8

Data are expressed as mean ± SD (n=8), LSD= least significant difference. Different letters indicate significant difference at (P≤0.05).

**Table 2.** Effects of NaNO<sub>2</sub> and R<sub>2</sub>Te on MCV, MCH and MCHC (mean ± SD, n=8)

Group	MCV(fL)	MCH(pg/cell)	MCHC(g/dL)
Control	57.17 ±3.3 a	16.42 ±0.9 ab	28.8 ±2.1 a
NaNO <sub>2</sub> (0.2%)	55.85 ±4.9 a	15.89 ±1.6 b	28.5 ±2.2 a
R <sub>2</sub> Te (11mg/kg) and NaNO <sub>2</sub> (0.2%)	57.81 ±2.9 a	17.40 ±0.9 a	30.1 ±1.3 a
R <sub>2</sub> Te (5.5mg/kg) and NaNO <sub>2</sub> (0.2%)	57.01 ±5.0 a	16.29 ±1.6 ab	28.5 ±1.2 a
R <sub>2</sub> Te (11mg/kg)	57.17 ±1.7 a	16.81 ±1.3 ab	29.4 ±1.9 a
LSD	NS	1.5	NS

LSD= least significant difference. Different letters indicate significant difference at (P≤0.05), NS= non-significant.

**Table 3.** Effects of NaNO<sub>2</sub> and R<sub>2</sub>Te on total and differential leukocyte count (mean ± SD, n=8)

Group	Leukocytes (×10 <sup>3</sup> /μL)	Neutrophils %	Lymph-cytes %	Mono-cytes %	Esino-phils %	Baso-phils %
Control	5.84±0.7 c	22.8±2.9 c	66.8±3.2 a	9.0±0.8 a	1.3±0.5 ab	0.3±0.5 a
NaNO <sub>2</sub> (0.2%)	8.66±0.8 a	29.3±1.6 a	60.0±1.5 c	8.8±0.5 a	1.5±0.5 a	0.5±0.5 a
R <sub>2</sub> Te (11mg/kg) &NaNO <sub>2</sub> (0.2%)	5.92±0.3 c	24.3±0.9 bc	65.5±1.2 ab	8.5±0.5 a	1.3±0.5 ab	0.5±0.5 A
R <sub>2</sub> Te (5.5mg/kg) &NaNO <sub>2</sub> (0.2%)	6.62±0.5 b	26.3±0.9 b	63.5±1.2 b	8.5±0.5 a	1.5±0.5 a	0.3±0.5 A
R <sub>2</sub> Te (11mg/kg)	6.35±0.5 Bc	23.8±1.6 c	66.0±2.4 a	9.1±0.6 a	0.9±0.6 b	0.3±0.5 A
LSD	0.67	2.5	2.5	0.7	0.6	NS

LSD= least significant difference. Different letters indicate significant difference at (P≤0.05), NS= non-significant.

## RESULTS

### Effects of NaNO<sub>2</sub> and R<sub>2</sub>Te on Hb concentration, Hct ratio, erythrocytes and platelets count:

The results in Table 1 revealed that sodium nitrite administration resulted in a significant decrease (P<0.05)

in hemoglobin concentration, Hct ratio, erythrocytes and platelets counts compared with control group. NaNO<sub>2</sub> induced changes in these parameters are ameliorated by R<sub>2</sub>Te administration the effects of NaNO<sub>2</sub> and their values approaches the values in the control group. It is clear that administration of R<sub>2</sub>Te alone does not affect these parameters.

### Effects of NaNO<sub>2</sub> and R<sub>2</sub>Te on MCV, MCH and MCHC

Table 2 shows no significant difference in MCV, MCH and MCHC among studied, except a significantly more MCH in R<sub>2</sub>Te (11mg/kg) and NaNO<sub>2</sub> group with NaNO<sub>2</sub> group (17.40 ±0.9 versus 15.89 ±1.6).

### Effects of NaNO<sub>2</sub> and R<sub>2</sub>Te on total and differential leukocyte counts

The results in Table 3 show a significant increase in total leucocytes count, and neutrophil percentage and significant decrease in lymphocyte percentage decrease in NaNO<sub>2</sub> group compared with control group. On the other hand, monocyte, eosinophil and basophil percentages were not affected. NaNO<sub>2</sub> induced changes on total and differential leukocyte counts are reversed by R<sub>2</sub>Te (11mg/kg) administration. The lower dose of R<sub>2</sub>Te (5.5mg/kg) is less effective in reversing the effects of NaNO<sub>2</sub> on total leukocytes count, neutrophil and lymphocyte percentages, these parameters are still significantly different from those in the control group. No significant difference in total, and differential leukocytes count were noticed between R<sub>2</sub>Te and control group.

## DISCUSSION

A significant decrease in erythrocytes count, Hb concentration and Hct ratio in rats administered sodium nitrite compared with control group was observed in this study (Table 1). Comparable results were reported in other studies (Avilez et al., 2004). Helal and Elsaid, 2006; Helal et al., 2008; Rahman et al., 2009). Nitrite in solution is highly absorbed from the gastrointestinal tract, and it is the first pass metabolism in the liver is low (Hunault et al., 2009). In the blood, nitrite mainly present in erythrocytes cytoplasm unbound to proteins (Dejam et al., 2005). Nitrite generates free radicals (Kohn et al., 2002; Abdel Baky et al., 2010) which oxidizes the ferrous ion in the Hb molecule leading to the formation of methemoglobin both *in vivo* (Chiodi and Mohler, 1987) and *in vitro* (Kohn et al., 2002). Nitrite induced hypoxia results from inability of met-Hb to transport oxygen, increased affinity of Hb to oxygen and possibly due to changes in the oxygen permeability of erythrocyte membranes (Shumilova et al., 2006). The nitrite, its metabolites, and lipid peroxidation products are thought to react with sulfhydryl groups of the lipid bilayer and protein components of red blood cells and change its structure (Maeda et al. 1987). Nitrate also induces changes in erythrocyte membranes to facilitate calcium entry. The increased intracellular calcium causes activation of phospholipases, which increases the phospholipids causing a rigid membrane (Kaya and Miura, 1982). Moreover, nitrite intoxication increases erythrophagocytosis by macrophages (Ivanova et al., 2011).

The decrease in erythrocyte count, Hb concentration and Hct ratio in this study may be attributed to intravascular lysis or shrinkage of erythrocytes or to the inhibition of erythropoiesis possibly as a consequence of the toxic effect of NaNO<sub>2</sub> on bone marrow, spleen and liver. Inhibition of intravascular hemolysis of erythrocytes and amelioration of toxic effects of sodium nitrite on the hematopoietic organs by bis 4-(4'-hydroxy-3'-methoxy-benzylideneaminophenyl) telluride may be attributed to its antioxidant and free radicals scavenging property (Kadhun et al., 2014).

Statistical analysis of hematological indices in comparison to those of control group reveals the presence of normocytic normochromic anemia in NaNO<sub>2</sub> group. This is indicated by the significant decrease in erythrocyte count, Hb concentration and Hct ratio and insignificant MCV, MCH, and MCHC (Table 1 and 2). Comparable results were reported in rats acutely and chronically intoxicated with sodium nitrite (Rahman et al., 2009; Bouaziz-Ketata et al., 2015). Normocytic normochromic anemia may result from NaNO<sub>2</sub> induced inhibition of erythropoiesis or from intravascular hemolysis (Rahman et al., 2009). Bis 4-(4'-hydroxy-3'-methoxy-benzylideneaminophenyl) telluride (R<sub>2</sub>Te) may inhibit intravascular hemolysis through inhibition of lipid peroxidation in erythrocytes membrane, thus increasing membrane resistance to spontaneous hemolysis.

Data in the present study showed a significant increase in leukocytes count and neutrophils percentage and a significant decrease in lymphocytes percentage in NaNO<sub>2</sub> group compared with control group (Table 3). Leukocytosis and neutrophilia have been observed in nitrate administered rats (Yarube and Ayo 2011; Bouaziz-Ketata et al., 2015). Leukocytosis also observed in rats acutely intoxicated with NaNO<sub>2</sub> (Miasoedova and Nazarov, 2003). Sodium nitrite inhibition of lymphocyte proliferation and reduction in lymphocyte percentage has been recorded by Abuharfeil *et al.* (2001). Leukocytosis may be attributed to the inflammatory response induced by sodium nitrite. This induces the release of a large number of cells from bone marrow, including neutrophils, which subsequently release large quantities of oxidants such as hydrogen peroxide which damages the adjacent tissues and cells (Abuharfeil *et al.* (2001). Modulation of NaNO<sub>2</sub> induced these changes by the novel organotellurium compound, bis 4-(4'-hydroxy-3'-methoxy-benzylideneaminophenyl) telluride, may be related to its anti-inflammatory effect that results from its free radical scavenging activity.

## CONCLUSION

The novel organotellurium compound (R<sub>2</sub>Te) is effective compound in ameliorating the toxic effects of sodium nitrite on haematological indices; this effect may be

attributed to its antioxidant and free radicals scavenging activity.

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