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ORIGINAL ARTICLE

# AMELIORATIVE EFFECTS OF PIROXICAM ON ANTHRACENE-INDUCED LUNG TOXICITY IN FEMALE *RATTUS NORVEGICUS*

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**Ethical considerations:** When reporting experiments on animals Observation of the ARRIVE guidelines 2.0: Updated guidelines for reporting animal research, published on July 14, 2020 (DOI: 10.1371/journal.pbio.3000410), is applied. The authors ensure that all procedures were performed in compliance with the guidelines for animal care of their institutions or with national/international guidelines.

## ABSTRACT

**Anthracene present in cigarette smoke may cause tumors of the lungs and other organs. Hence, the therapeutic potential of piroxicam against anthracene-induced lung damage was investigated. Thirty-six female rats, aged seven weeks, were randomly divided into six groups of six rats per group and administered 100 mg/kg of oral anthracene, except the control group that received 2.5 mg/kg of water only, for a period of three consecutive weeks. After 24 hours, the rats were treated daily with different doses of piroxicam, carboplatin, and a combination of both for the next three consecutive weeks. Body weights and blood samples (2 ml) were obtained weekly. After 24 hours, the rats were euthanized with 100 mg/kg intraperitoneal sodium pentobarbitone. The lungs, kidneys, liver, and heart excised and weighed for allometric scaling significantly decreased ($p < 0.05$), except those treated with carboplatin and/or piroxicam. Serum carcinoembryonic antigen increased significantly in the piroxicam-treated group, whereas total oxygen consumption, heart rate, ventilation rate, lung volume, and tidal volume were significantly decreased ($p < 0.05$) in the anthracene-administered groups. Lung width was significantly decreased ($p < 0.05$) in experimental groups. Potential doubling time, growth factor, and cell loss factor were significantly increased ($p < 0.05$). Carboplatin remitted micronodular pulmonary lesions, and piroxicam reduced the lesions.**

**Keywords: anthracene; amelioration; carboplatin; lung damage; piroxicam; rat**

## INTRODUCTION

Lung cancer is currently one of the most common and deadliest forms of cancer worldwide. The average life expectancy of patients after diagnosis is typically between three and seven months [1]. Approximately 2.48 million new cases and 1.8 million deaths from lung cancer were reported in 2022, and this burden is projected to increase to 4.62 million new cases and 3.55 million deaths by 2050 [2]. An estimated 18 million cancer cases were recorded worldwide in 2018, including 9.5 million (52.8%) in men and 8.5 million (47.2%) in women, indicating a higher incidence and lower life expectancy among men [3]. In 2008, cancers accounted for an estimated 169.3 million disability-adjusted life years (DALYs) lost globally [4]. African countries recorded approximately 541,800 cancer-related deaths, representing about 0.3% of global cases [5]. In Nigeria, an estimated 100,000 new cancer cases occur annually, with a high case-fatality rate [6]. The country contributed about 15% (102,150 cases) of the 681,000 new cancer cases reported across Africa in 2008 [7]. The incidence of lung cancer in Nigeria is approximately 1.4%, ranking 14th among 35 types of cancers reported in the country [8]. Cigarette smoking, which exposes individuals to polycyclic aromatic hydrocarbons (PAHs) such as anthracene, remains a major risk factor for lung cancer. More than 80% of lung cancer cases are diagnosed after the age of 50 years [9].

Piroxicam is a nonsteroidal anti-inflammatory drug (NSAID) used in both humans and animals to relieve pain and fever and to treat inflammatory and rheumatic disorders, including mastitis [10]. It is highly bound to plasma proteins, has a biological half-life of approximately 50 hours in humans, and is excreted mainly in urine and feces [11]. In addition, piroxicam has been reported to offer protection against cerebral ischemia [12] and to exert hypotensive and sedative effects [13]. The central nervous system (CNS) effects of piroxicam have been attributed to metabolites formed through keto–enol tautomerism [14]. The median lethal dose ($LD_{50}$) of piroxicam has been reported to be less than 500 mg/kg in mice and rats and less than 1000 mg/kg in guinea pigs, chickens, monkeys, turkeys, and dogs [13]. Piroxicam has also demonstrated anticancer activity against transitional cell carcinoma [15]. Piroxicam suppresses tumor growth and malignant transformation [16] through the inhibition of cyclooxygenase, phosphodiesterase, and protein kinases, which are central to cancer initiation and promotion. It also interferes with transmembrane ion fluxes and cell-to-cell adhesion [17].

Anthracene is a solid polycyclic aromatic hydrocarbon (PAH) consisting of three fused benzene rings, commonly derived from coal tar. It has a molecular weight of 178.23 g/mol [16–18] and is generated during incomplete combustion processes. Human exposure occurs mainly through tobacco smoke and the ingestion of food contaminated with combustion by-products. Anthracene is a three-ring, semi-volatile compound [19], readily biodegraded in soil and susceptible to photodegradation in the presence of light [20]. However, data on its toxicity potential remain limited, although prolonged exposure has been associated with both topical and systemic adverse effects. Carcinogenicity bioassays involving anthracene in humans and experimental models have generally yielded positive results [21].

Cancer therapy over the past five decades has imposed a substantial global economic burden, estimated at over 900 billion USD, surpassing that of cardiovascular diseases [22, 23]. This underscores the need for the discovery of new drugs or the repurposing of existing NSAIDs for the treatment of anthracene-induced lung tumors. Despite the poor prognosis of lung cancer, metastasis and the lack of ideal therapeutic regimens remain major clinical challenges [24]. The present study was therefore designed to evaluate the potential of repurposing piroxicam (an NSAID) for the treatment of anthracene-induced lung tumors, given its long half-life and strong anti-inflammatory and immunomodulatory properties. Female rats were used in this study, as sex-related differences in susceptibility to chemically induced tumors have been reported in several experimental models [25].

## MATERIALS AND METHODS

### Drugs

Piroxicam (Shanxi Federal Pharmaceutical Co. Ltd., China; NAFDAC No. 04-6809) and carboplatin (German Pharmaceutical Company Ltd., Germany) were used for the experiment. Carcinoembryonic antigen (CEA) assay kits (AccuQink, India) were employed as a model tumor biomarker in this study.

**Animals**

Thirty-six female rats aged seven weeks and weighing 166.25 g ± 26.7 g were housed under a 12-hour light–dark cycle in the Animal House of the Department of Veterinary Physiology and Biochemistry, College of Veterinary Medicine, Joseph Sarwuan Tarka University, Makurdi, Benue State, Nigeria. Feed and water were provided ad libitum. The animals were cared for in accordance with the guidelines of the College Ethical Committee (Permit No. JOSTUM/CVM/ETHICS/2025/07).

**Preparation of piroxicam solution**

Approximately 20 g of piroxicam granules obtained from capsules were dissolved in 80 ml of distilled water to prepare a 20% (w/v) solution (equivalent to 200 mg/ml). The resulting preparation was a homogeneous and stable solution with a pH of approximately 6.

**Selection of therapeutic doses**

The therapeutic doses of piroxicam were selected based on a pilot study conducted in rats. Reported $LD_{50}$ values from the literature were used as reference [13].

**Selection of tumor-inducing dose of anthracene**

Anthracene was used to induce tumor formation in rats. A dose of 100 mg/kg body weight was selected as the induction dose, corresponding to 2% of the reported oral $LD_{50}$ (>5000 mg/kg body weight) [26]. The compound was administered orally once daily for 21 consecutive days.

**Translation of human therapeutic dose to rat dose**

The human equivalent dose (HED) formula was employed to extrapolate the therapeutic doses of carboplatin and piroxicam from humans to rats, following the method described in the literature [13].

$$HED(mg/kg) = \frac{Animal\ dose(mg/kg) \times Animal\ km}{Human\ km} \quad \text{.....(i)}$$

$$Km = \frac{Body\ weight}{Body\ surface\ area} \quad \text{..... (ii)}$$

Calculation of the dose of piroxicam was done according to reported methods [13, 27].

Weight of rats = 166.25 g

Weight of human = 60 kg

Hkm = 37.5

RKm = 6.7

$$HED(mg/kg) = \frac{RD\ x\ RKm}{HKm} \quad \text{.....(iii)}$$

RD = rat dose; RKM = rat metabolism constant; HKM = human metabolism constant

$$\frac{RD\,x\,6.7}{37.5}$$

$$\therefore RD\,x\,6.7 = 20\,x\,37.5$$

$$RD = \frac{20\,x\,37.5}{6.7} = 111.9\,mg/kg$$

$$2\%\ of\ therapeutic\ dose = \frac{2}{100}\,x\,111.9 = 2.238 \simeq 2.0\,mg/kg$$

But $LD_{50}$ of piroxicam in rat = 259.4 ± 69.6 mg/kg which is 189.8 to 329.

$$2\%\ of\ LD_{50} = \frac{2}{100}\,x\,\frac{259.4}{1} = 5.188 \simeq 5.0\,mg/kg$$

Hence therapeutic dose of 2–5 mg/kg was chosen for piroxicam treatment.

The therapeutic doses of carboplatin were estimated based on previously reported toxicological data [27, 28]. Considering the reported oral $LD_{50}$ value of 343 mg/kg in rats, 1–2% of this value (equivalent to 3.43–6.86 mg/kg) was selected as a safe and pharmacologically active dose range. Accordingly, two doses of 2.5 mg/kg and 5.0 mg/kg were chosen for comparative evaluation of efficacy and safety.

**Experimental induction of lung tumorigenesis**

A randomized repeated-measures experimental design was adopted. Thirty-six female rats were randomly assigned to six groups of six animals each. Groups 1, 3, 4, 5, and 6 received oral anthracene (100 mg/kg body weight) daily for three weeks to induce lung tumor formation, whereas Group 2 served as the negative control and received 2.5 mL of distilled water only. Baseline (pretreatment) blood samples (2 mL) were collected from each rat before anthracene or water administration, and additional samples were taken on days 7 and 21. Following the induction phase (day 0–21), the rats were treated orally for 21 consecutive days (days 22–42) as follows: Groups 1 and 2 received distilled water (vehicle control), Groups 3 and 4 received piroxicam (2.5 mg/kg and 5.0 mg/kg, respectively), Group 5 received carboplatin (2.5 mg/kg), and Group 6 received a combination of piroxicam (2.5 mg/kg) and carboplatin (2.5 mg/kg).

Hence 3.43–6.86 mg/kg was calculated. So, we decided to use 2.5 and 5.0 mg/kg for the two for comparative efficacy and safety.

| Group | Drugs used |
|---|---|
| 1 | Tumor control group (anthracene, water) |
| 2 | Normal control group (no anthracene, water) |
| 3 | Piroxicam low-dose group (2.5 mg/kg) (anthracene, piroxicam) |
| 4 | Piroxicam high-dose group (5.0 mg/kg) (anthracene, piroxicam) |
| 5 | Carboplatin group (2.5 mg/kg) (anthracene, carboplatin) |
| 6 | Combination therapy group (piroxicam 2.5 mg/kg + carboplatin 2.5mg/kg) (anthracene, piroxicam, carboplatin) |

Anthracene administration for tumor induction was discontinued after 21 days. All therapeutic treatments commenced on day 22 of the study and continued for 21 consecutive days. Throughout this period, the normal control group (Group 2) continued to receive distilled water only, without anthracene or drug treatment. On day 42, all animals were humanely euthanized by intraperitoneal injection of sodium pentobarbital (100 mg/kg body weight) for gross pathological and histopathological examination [29–31].

**Analysis of tumor biomarker**

Serum concentrations of carcinoembryonic antigen (CEA) were determined using an automated chemiluminescent immunoassay, as follows. Serum samples were transferred into individual cuvettes containing superparamagnetic microbeads coated with anti-CEA monoclonal antibodies. CEA in the samples was bound to the antibodies on the surface of the magnetic beads, and a magnetic field was applied to separate bound components from unbound components. Unbound substances were then washed away, and a second anti-CEA antibody labeled with alkaline phosphatase was added. The labeled antibody bound to a different epitope on the CEA molecule, forming a sandwich complex. The magnetic beads were again separated magnetically, and unbound labeled antibodies were removed by washing. Substrate reagents were then added to initiate a chemiluminescent reaction catalyzed by alkaline phosphatase, resulting in light emission. The light intensity was measured using a luminometer. The assay was performed using the AccuBind CEA chemiluminescent ELISA kit (Monobind Inc., USA). The analytical sensitivity (limit of detection) of the assay was 0.5 ng/mL, as specified by the manufacturer. Reference intervals for CEA were defined as follows: <3.0 ng/mL (normal, non-smokers), ≥5.0 ng/mL (abnormal), 5–10 ng/mL (slightly elevated), 10–20 ng/mL (significantly elevated), and >20 ng/mL (indicative of metastasis) [32]. Precision and performance characteristics, including repeatability, reproducibility, accuracy, linearity, analytical range, limit of detection, interference, specificity, carry-over, and reference interval verification, were validated according to the manufacturer's guidelines. All analyses were performed in triplicate.

**Allometric scaling of pathophysiological and tumor parameters**

The micronodular lesions, weight, length, width, and volume of the left and right lungs of the experimental rats were measured using a metric ruler and electronic balance. Allometric relationships between organ size and body weight were analyzed using the general allometric equation: $Y = aM^b$, where Y is the biological variable (e.g., organ weight or volume), M is the measure of body size (body weight), a is a proportionality constant, and b is the allometric scaling exponent. The weights of the kidneys, liver, spleen, and heart were also determined using an electronic analytical balance [33, 34].

**Lung tumor kinetic parameters**

Tumor growth parameters were calculated mathematically according to the method described by Saganuwan [34]. The parameters determined included tumor radius, volume, weight, doubling time, specific growth rate, cell proliferation rate (cells/day), labeling index, growth fraction, potential doubling time, and cell loss factor. These parameters were computed using the following equations [34].

$$Tumor\ volume\ (cm^3) = \frac{4}{3} x \pi x r^3 \quad \text{.....(iv)}$$

Where $\pi = 3.14159$ ' $r = \frac{d}{2}$, r = radius; d = diameter

$$Tumor\ volume\ index\ (V, mm^3) = \frac{a \times b^2}{2} \quad \text{.....(v)}$$

where a = tumor length (mm) and b = tumor width (mm). Tumor doubling time (per day) = 1g of tumor mass = $10^9$ cells = 30 doubling time

$$Specific\ Growth\ Rate\ (SGR)\ (\%/day) = \frac{ln_2 x\ 100}{DT} \quad \text{.....(vi)}$$

DT = tumor doubling time; $ln_2 = 0.6931$

$$Cell\ cycle\ per\ day\ (day) = \frac{TW\ x\ 10^9}{1000} \quad \text{..... (vii)}$$

TW = tumor weight

$$Growth\ factor = \frac{P}{Q+P} \quad \text{(viii)}$$

$$Cell\ loss\ factor\ (\varphi, \%) = \frac{1 - DTpot}{DT} \quad \text{(ix)}$$

$$Potential\ doubling\ time\ (Tpot, days) = \frac{Tc}{GF} \quad \text{(x)}$$

where Tc = duration of the cell cycle (days), and GF = growth fraction (P/(P+Q)).

$$Tumor\ \log_{10}\ cell\ kill = \frac{T - C}{3.32\ XTd} \quad \text{(xi)}$$

Tc = duration of the cell cycle constant = 3.32; T–C = difference in time (days) for a treated tumor size compared to untreated (control); Td = tumor doubling time, P = proliferating cells; Q = quiescent cells.

**Determination of metabolic and cardiorespiratory parameters**

Oxygen consumption, lung ventilation rate, lung volume, tidal volume, blood volume, respiratory frequency, heart rate, and organ weights (lungs and heart) were estimated using allometric equations derived from body mass data obtained in this study [35].

Metabolic rate (Kcal/day): 3.52 $W^{0.75}$ (where W = body weight in kilograms) ..... (xii)
Total $O_2$ consumption, $V_{02}$ (liter $O_2$ $h^{-1}$: 0.676 x $Mb^{0.75}$
(where Mb = body mass in kilogram) ..... (xiii)
Body mass is the total amount of matter in the body measured in kilograms.
$O_2$ consumption per kilogram (liter $h^{-1}$ kg):
0.676 x $Mb^{-0.25}$ .....(xiv)
Heart rate ($min^{-1}$): 241 x $Mb^{0.25}$ .....(xv)
Lung ventilation rate (liter $h^{-1}$): 20.0 x $Mb^{0.75}$ .....(xvi)
Lung volume (liter): 0.063 x $Mb^{1.02}$ ..... (xvii)
Tidal volume (liter): 0.0062 x $Mb^{1.01}$ ..... (xviii)
Respiratory frequency ($min^{-1}$): 53.5 x $Mb^{-0.26}$ .....(xix)

The calculated parameters were verified to ensure consistency with the established allometric equations.

**Statistical analyses**

The modified Kaplan-Meier estimate

$$\equiv \frac{Number\ of\ surviving\ tumor\ cells - Number\ of\ dead\ tumor\ cells}{Number\ of\ surviving\ tumor\ cells}$$

was used, which relates the number of surviving and dead tumor cells [34]. Data were expressed as mean ± standard error of mean (SEM). Differences between groups and time points were analyzed using two-way repeated-measures analysis of variance (ANOVA), followed by the least significant difference (LSD) post hoc test to determine pairwise differences at a 5% significance level ($p < 0.05$). Statistical analyses were performed using standard formulas as described by Saganuwan [36].

## RESULTS

**Body and organ weights**

The body weight of the female rats induced with anthracene and treated with high-dose piroxicam (Group 4) was significantly higher at day 42 in Group 4 ($p < 0.05$) on day 42 (162.97 ± 4.15 g) compared with Groups 1 (150.62 ± 2.39 g), 2 (138.89 ± 1.15 g), 3 (136.61 ± 2.57 g), 5 (148.30 ± 2.25 g), and 6 (141.53 ± 1.95 g) (Table 1). The mean weight of the lungs was significantly greater ($p < 0.05$) in Group 6 (0.87 ± 0.03 g) compared with Groups 1 (0.62±0.10 g), 2 (0.55 ± 0.06 g), 3 (0.74 ± 0.11 g), 4 (0.64 ± 0.10 g), and 5 (0.73 ± 0.06 g). Similarly, the mean weights of the kidneys (0.61 ± 0.04 g), liver (3.82 ± 0.81 g), spleen (1.16 ± 0.00 g), and heart (0.64 ± 0.00 g) in Group 6 were significantly higher ($p < 0.05$) compared with Group 2 (kidneys: 0.47 ± 0.03 g; liver: 2.93 ± 0.29 g; spleen: 1.13 ± 0.31 g; heart: 0.51 ± 0.03 g). Among the organs, the liver had the greatest mean weight, followed by the spleen, lungs, heart, and kidneys (Table 2).

**Lung morphology and micronodular lesions**

The effects of anthracene and piroxicam on lung dimensions and micronodular lesions in female rats are summarized in Table 3.

In all groups, the left lungs were generally longer than the right lungs ($p < 0.05$), with mean left lung lengths ranging from 2.10 ± 0.10 cm (Group 6) to 2.67 ± 0.33 cm (Group 1). Right lung lengths ranged from 1.75 ± 0.15 cm (Group 6) to 2.15 ± 0.35 cm (Group 3). Differences in lung width followed a similar pattern, with slightly larger values recorded for the left lung in most groups.

The dimensions of pulmonary micronodules were significantly greater ($p < 0.05$) in Groups 1 and 2 compared with all treated groups. In contrast, micronodule size was markedly reduced in Groups 3, 4, and 5 and completely

**Table 1. Effects of anthracene and piroxicam on body mass (g) of female rats**

| Group number | Experimental Groups | Days of Treatments | | | | |
|---|---|---|---|---|---|---|
| | | 0 | 7 | 21 | 35 | 42 |
| 1. | Induced not treated Water (2.5ml) | 149.36±1.68$^{bd}$ | 150.62±1.66$^{bd}$ | 162.91±1.58$^{ab}$ | 148.60±3.66$^{bd}$ | 150.62±2.39$^{bd}$ |
| 2. | Neither induced nor treated Water(2.5ml) | 145.83±1.81$^{bd}$ | 148.85±1.83$^{ad}$ | 146.32±1.98$^{bd}$ | 135.65±1.30$^{bd}$ | 138.89±1.15$^{bd}$ |
| 3. | Induced and treated Piroxicam (2.5mg/kg) | 147.46±1.06$^{bd}$ | 150.12±0.96$^{ad}$ | 147.21±1.95$^{bd}$ | 135.98±2.50$^{bd}$ | 136.61±2.57$^{bd}$ |
| 4. | Induced and treated Carboplatin (2.5mg/kg) Piroxicam (2.5mg/kg) | 147.97±1.01$^{bd}$ | 150.74±1.01$^{bd}$ | 134.02±2.81$^{bd}$ | 155.07±3.86$^{bc}$ | 162.97±4.15$^{ac}$ |
| 5. | Induced and treated Piroxicam (5mg/kg) | 152.13±1.67$^{bc}$ | 154.25±1.65$^{ac}$ | 180.62±3.20$^{ac}$ | 148.45±2.17$^{bd}$ | 148.30±2.25$^{bd}$ |
| 6. | Induced and treated Carboplatin(2.5mg/kg) | 151.75±0.92$^{bd}$ | 153.51±0.94$^{ad}$ | 142.63±1.43$^{bd}$ | 137.39±1.69$^{bd}$ | 141.53±1.95$^{bd}$ |

Keys: a = significantly higher along the row ($p < 0.05$); b = significantly lower along the row ($p < 0.05$); c = significantly higher along the column ($p < 0.05$); d = significantly lower along the column ($p < 0.05$); Mass = is the amount of matter in a material (e.g body)

**Table 2. Weights (g) of some internal organs of the female rats treated with anthracene and piroxicam**

| Group number | Experimental Groups | Internal Organs (g) | | | | |
|---|---|---|---|---|---|---|
| | | Lung | Kidney | Liver | Spleen | Heart |
| 1. | Induced not treated Water (2.5ml) | 0.62±0.10$^{bd}$ | 0.54±0.04$^{bd}$ | 3.92±1.06$^{ac}$ | 0.64±0.08$^{bd}$ | 0.59±0.10$^{bd}$ |
| 2. | Neither induced nor treated Water(2.5ml) | 0.55±0.06$^{bd}$ | 0.47±0.03$^{bd}$ | 2.93±0.29$^{ad}$ | 1.13±0.31$^{bd}$ | 0.51±0.03$^{bd}$ |
| 3. | Induced and treated Piroxicam (2.5mg/kg) | 0.74±0.11$^{bd}$ | 0.54±0.03$^{bd}$ | 2.96±0.24$^{ad}$ | 0.97±0.21$^{bd}$ | 0.62±0.06$^{bd}$ |
| 4. | Induced and treated Carboplatin (2.5mg/kg) Piroxicam (2.5mg/kg) | 0.64±0.10$^{bd}$ | 0.48±0.08$^{bd}$ | 2.97±0.37$^{ad}$ | 0.91±0.04$^{bd}$ | 0.65±0.14$^{bc}$ |
| 5. | Induced and treated Piroxicam (5mg/kg) | 0.73±0.06$^{bd}$ | 0.49±0.04$^{bd}$ | 2.81±0.11$^{ad}$ | 1.07±0.21$^{bd}$ | 0.52±0.14$^{bd}$ |
| 6. | Induced and treated Carboplatin (2.5mg/kg) | 0.87±0.03$^{bc}$ | 0.61±0.04$^{bc}$ | 3.82±0.81$^{ad}$ | 1.16±0.00$^{bc}$ | 0.64±0.00$^{bd}$ |

Keys: a = significantly higher along the row ($p < 0.05$); b = significantly lower along the row ($p < 0.05$); c = significantly higher along the column ($p < 0.05$); d = significantly lower along the column ($p < 0.05$)

**Table 3. Dimensions of lung and micronodular lesions of rats administered anthracene and treated with piroxicam and carboplatin**

| Group number | Experimental Groups | Lung Parameters (cm) | | | | |
|---|---|---|---|---|---|---|
| | | Right lung | Left lung | Width of right lung | Width of left lung | Nodule |
| 1. | Induced not treated Water (2.5ml) | 2.00±0.19$^{bd}$ | 2.67±0.33$^{ac}$ | 1.23±0.23$^{ad}$ | 1.50±0.25$^{bd}$ | 0.28±0.09$^{bc}$ |
| 2. | Neither induced nor treated Water (2.5ml) | 2.10±0.20$^{bd}$ | 2.30±0.30$^{ad}$ | 1.45±0.45$^{bd}$ | 1.45±0.35$^{bd}$ | 0.28±0.04$^{bc}$ |
| 3. | Induced and treated Piroxicam (2.5mg/kg) | 2.15±0.35$^{bc}$ | 2.50±0.10$^{ad}$ | 1.45±0.05$^{bd}$ | 1.60±0.10$^{bc}$ | 0.20±0.04$^{bd}$ |
| 4. | Induced and treated Carboplatin (2.5mg/kg) Piroxicam (2.5mg/kg) | 2.15±0.05$^{bd}$ | 2.25±0.05$^{ad}$ | 1.10±0.10$^{bd}$ | 1.45±0.05$^{bd}$ | 0.24±0.04$^{bd}$ |
| 5. | Induced and treated Piroxicam (5mg/kg) | 2.05±0.05$^{bd}$ | 2.15±0.15$^{ad}$ | 1.05±0.05$^{bd}$ | 1.20±0.10$^{bd}$ | 0.20±0.06$^{bd}$ |
| 6. | Induced and treated Carboplatin (2.5mg/kg) | 1.75±0.15$^{bd}$ | 2.10±0.10$^{ad}$ | 1.65±0.15$^{bc}$ | 1.50±0.00$^{bd}$ | 0.00±0.00$^{bd}$ |

Keys: a = significantly higher along the row ($p < 0.05$); b = significantly lower along the row ($p < 0.05$); c = significantly higher along the column ($p < 0.05$); d = significantly lower along the column ($p < 0.05$)

absent in Group 6, indicating a dose-dependent and synergistic effect of piroxicam and carboplatin on regression of lung lesions (Table 3).

**Tumor kinetic parameters**

The calculated tumor-kinetic parameters are summarized in Table 4. Rats in Group 1 (anthracene only, no treatment) exhibited the largest tumor dimensions, with a mean tumor diameter of 2.8 ± 0.9 mm, volume of 1149.1 ± 38.2 $mm^3$, and weight of 548.8. ± 18.2 mg. These values were significantly higher ($p < 0.05$) than those recorded in the treatment groups.

In comparison, rats treated with low-dose piroxicam (Group 3) showed markedly smaller tumors (radius 1.0 ± 0.2 mm; volume 418.8 ± 3.4 $mm^3$; weight 200.0 ± 1.6 mg), while those treated with high-dose piroxicam (Group 5) or 2.5 mg/kg carboplatin (Group 4) exhibited intermediate values. The combination treatment (Group 6) produced complete tumor regression, with no measurable tumor mass.

Tumor doubling time (TDT) was longest in Group 1 (164.6 ± 5.5 days) and shortest in the treated groups (60–104 days), whereas specific growth rate (SGR) and cell production per day followed the reverse trend.

Calculated potential doubling time was approximately 5.1 days for all groups except Group 6, which showed complete remission (0 days). Tumor cell kill was estimated at 0% for Groups 1 and 2, 14.3% for Group 4, 28.6% for Groups 3 and 5, and 100% for Group 6. The theoretical growth factor was 0.59 for all groups except Group 6 (0.00). The cell loss factor was estimated at 2.4% for Groups 1 and 2, 3.4% for Group 4, 6.8% for Groups 3 and 5, and 0% for Group 6.

**Carcinoembryonic antigen (CEA)**

Serum levels of carcinoembryonic antigen (CEA) increased significantly ($p < 0.05$) in all rats treated with anthracene by day 21 compared with the normal control group (Table 5). The mean CEA concentrations at day 21 and day 42 were as follows: Group 1 (2.48 ± 0.72 vs. 1.40 ± 0.18 µg/mL), Group 2 (3.51 ± 0.07 vs. 3.37 ± 0.06 µg/mL), Group 3 (4.08 ± 0.12 vs. 3.76 ± 0.11), Group 4 (3.59 ± 0.48 vs. 2.67 ± 0.08 µg/mL), Group 5 (2.59 ± 0.89 vs. 1.87 ± 0.46), and Group 6 (3.92 ± 0.07 vs. 2.78 ± 0.30 µg/mL. By day 42, CEA concentrations had generally returned to near pretreatment (baseline) levels, indicating partial or complete remission of anthracene-induced lesions following piroxicam and carboplatin treatment.

**Cardiorespiratory parameters**

Oxygen consumption was significantly higher ($p < 0.05$) on day 21 in group 5 (346.8 ± 6.14 $L/h^{-1}Kg^{-1}$) in comparison to group 1 (312.8 ± 30.4 $mLh^{-1}$), 2 (281.0 ± 38.1 $mLh^{-1}$), 3 (282.7 ± 37.4 $mLh^{-1}$), 4 (266.9 ± 53.8 $mLh^{-1}$), and 6 (273.9 ± 27.4 $mLh^{-1}$), respectively. Total oxygen consumption was significantly increased ($p < 0.05$) on day 42 in group 2 (30.00 ± 0.00 mL/kg/min) as compared to groups 1, 3, 4, 5 (10.00 ± 0.00 mL/kg/min), and 6 (20.00 ± 0.00 mL/kg/min), respectively. Heart rate was significantly increased ($p < 0.05$) on day 42 in group 4 (865.38 ± 5.48 beats/min) as compared to groups 1 (842.95 ± 4.56 beats/min), 2 (820.46 ± 3.57 beats/min), 3 (815.95 ± 4.67 beats/min), 5 (838.59 ± 4.47 beats/min), and 6 (825.64±4.26 beats/min), respectively. Ventilation rate was significantly higher ($p < 0.05$) on day 42 in group 4 (925.98 ± 235.51 l/h) in comparison to that of rats in group 1 (855.82 ± 136.2 l/h), 2 (789.15 ± 65.26 l/h), 3 (776.21 ± 145.90 l/h), 5 (842.62 ± 128.06 l/h), and 6 (804.17 ± 110.69 l/h), respectively. Lung volume was significantly increased ($p < 0.05$) on day 42 in group 4 (11.60 ± 1.80 ml) as compared to groups 1 (10.42 ± 0.86 ml), 2 (9.33 ± 0.31 ml), 3 (9.13 ± 0.94 ml), 5 (10.20 ± 0.78 ml), and 6 (9.57 ± 0.65 ml), respectively. Nevertheless, tidal volume was significantly increased ($p < 0.05$) in group 4 (1.08 ± 0.17 ml) in comparison with groups 1 (0.97 ± 0.08 ml), 2 (0.87 ± 0.03 ml), 3 (0.85 ± 0.17 ml), 5 (0.95 ± 0.07 ml), and 6 (0.89 ± 0.62 ml), respectively. Meanwhile, frequency of respiration increased significantly ($p < 0.05$) on day 42 from 1.56 ± 0.09 to 2.87 ± 0.09 in group 2 and decreased significantly in group 1 from 1.72 ± 0.09 to 1.07 ± 0.79 $sec^{-1}$, group 3 from 1.19 ± 0.09 to 0.98 ± 0.09 $sec^{-1}$, 4 (from 1.41 ± 0.09 to 0.52 ± 0.09 $sec^{-1}$), 5 (from 1.74 ± 0.09 to 1.17 ± 0.09 $sec^{-1}$, and 6 (from 1.86 ± 0.09 to 1.42 ± 0.10 $sec^{-1}$), respectively (Table 6).

## DISCUSSION

**Body and organ weights**

The decreased body weight of the animals observed during the study shows that either anthracene or piroxicam can cause a decrease in body weight gain of female

**Table 4. Kinetic parameters of anthracene-induced lung tumor in rats**

| Group Number | Experimental Groups | Diameter (mm) | Radius (mm) | TV (mm3) | TW (mg) | Kinetic parameter of lung tumor | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | TDT (day) | SGR (%/d) | CCD (day) | GF | TCK (%) | TQCs | TCP | DTpot (day) | CLF (%) |
| **1.** | Induced treated with water (2.5mg/kg) | 2.8±0.9$^{a}$ | 1.4±0.5$^{a}$ | 1149.1±38.2$^{a}$ | 548.8±18.2$^{a}$ | 164.6±5.5$^{a}$ | 0.42$^{a}$ | 5.5x10$^{8a}$ | 0.59 | 0.0 | 1.96x10$^{8}$ | 2.8X10$^{8}$ | 5.1 | 2.4 |
| **2.** | Non-induced treated with water (2.5mg/kg) | 2.8±0.4 | 1.4±0.2 | 1149.1±3.4 | 548.8±1.6 | 164.6±0.5 | 0.42 | 5.5x10$^{8b}$ | 0.59 | 0.0 | 1.96x10$^{8}$ | 2.8X10$^{8}$ | 5.1 | 2.4 |
| **3.** | Induced treated piroxicam (2.5mg/kg) | 2.0±0.4$^{b}$ | 1.0±0.2$^{b}$ | 418.8±3.4$^{b}$ | 200.0±1.6$^{b}$ | 60.0±0.5$^{b}$ | 1.2$^{b}$ | 2 x10$^{8b}$ | 0.59 | 28.6 | 1.4x10$^{8}$ | 2.0X10$^{8}$ | 5.1 | 6.8 |
| **4.** | Induced treated carboplatin (2.5mg/kg), piroxicam (2.5mg/kg) | 2.4±0.4$^{b}$ | 1.2±0.2$^{b}$ | 723.6±3.4$^{a}$ | 345.6±1.6$^{b}$ | 103.7±0.5$^{b}$ | 0.7$^{b}$ | 3.5x10$^{8b}$ | 0.59 | 14.3 | 1.68x10$^{8}$ | 2.4X10$^{8}$ | 5.1 | 3.4 |
| **5.** | Induced treated piroxicam (5mg/kg) | 2.0±0.6$^{b}$ | 1.0±0.3$^{b}$ | 418.8±11$^{b}$ | 200.0±5.4$^{b}$ | 60.0±1.6$^{b}$ | 1.2$^{b}$ | 2 x10$^{8b}$ | 0.59 | 28.6 | 1.4x10$^{8}$ | 2.0X10$^{8}$ | 5.1 | 6.8 |
| **6.** | Induced treated carboplatin (2.5mg/kg) | 0.0±0.0$^{b}$ | 0.0±0.0$^{b}$ | 0.00±0.0$^{b}$ | 0.0±0.0$^{b}$ | 0.0±0.0$^{b}$ | 0.0$^{b}$ | 0.0x10$^{8b}$ | 0.00 | 100 | 0.0 | 0.0 | 0.0 | 0.0 |

Keys: TV = tumor volume; TW = tumor weight; TDT = tumor doubling time; SGR = specific growth rate; CCD = cell cycle per day; TCK = tumor cell kill; GF = growth factor; CLF = cell loss factor; DTpot = doubling time potential; a= significantly higher along the column ($p>0.05$); b = significantly lower along the column ($p < 0.05$); 1g of tumor cells = 1 cm = 109 tumor cells; TDT for adenocarcinomas = 170 days; TCP = tumor cells population; period of induction = 21 days; In every 1000 lung tumor cells 600 to 800 are quiescent, hence 700 cells were chosen in the present study; TQCs = tumor quiescent cells; Tc = duration of cell cycle = 2–4 days, hence 3 days was chosen. Tumor cell kill was calculated with reference to tumor size and control group.

rats, which could be attributed to systemic toxicity, metabolic alteration, and reduced appetite. This agrees with the report indicating that piroxicam is antiproliferative [37]. However, the administration of anthracene/piroxicam increased weight gain, suggesting an antagonistic effect which is hormetic. Piroxicam affects the synthesis of DNA, which in turn affects protein synthesis [38]. The increased organ weight gain observed for the carboplatin as compared to the piroxicam-treated group shows that carboplatin may cause weight gain [39]. Decreased body mass caused by anthracene and carboplatin shows that the drugs could be used against obesity. The effects could be drug and dose-dependent. However, the increased body mass observed in the group administered carboplatin/piroxicam suggests that administration of the drugs could be used for management of weight loss [40].

### The effects of anthracene, carboplatin, and piroxicam on morphological parameters of rat lung tumor

Presence of nodular lesions observed in all the groups except the group administered carboplatin only shows that group administered carboplatin could be used to treat lung micronodular lesions caused by anthracene. However, 5 mg/kg of piroxicam or 2.5 mg/kg of piroxicam in combination with carboplatin (2.5 mg/kg) reduced the micronodular lesion, which translates to decreased tidal volume and frequency of respiration observed in the present study [41]. This finding agrees with the report indicating that combination therapy that includes carboplatin (2.5 mg/kg) could improve survivability in lung cancer [42]. Calculation of carboplatin dose based on estimating glomerular filtration rate (eGFR) provides optimal therapeutic effect [43].

### The effects of anthracene, piroxicam, and carboplatin on the kinetics of lung tumors

The tumor remission caused by piroxicam is corroborated by the report of Knapp et al., indicating that piroxicam has antitumor activity that may not be directly cytotoxic [44]. Also, the lung tumor remission caused by piroxicam/carboplatin in the present study agrees with the report indicating that the combination could induce tumor remission [45]. Hence, a combination of carboplatin (2.5 mg/kg) and piroxicam (2.5 mg/kg) could be highly beneficial in the management of lung cancer. Therefore, small cell carcinoma of the bladder and lung may have a convergent but different pathogenesis [46], suggesting pros-

**Table 5. Effects of anthracene and piroxicam on carcinoembryonic antigen (CEA) of female rats**

| Group number | Experimental Groups | Carcinoembryonic antigen (µg/ml) | | |
|---|---|---|---|---|
| | | 0 | 21 | 42 |
| **1.** | Induced not treated Water (2.5ml) | $1.40\pm0.18^{bd}$ | $2.48\pm0.72^{ad}$ | $1.40\pm0.18^{bd}$ |
| **2.** | Neither induced nor treated Water (2.5ml) | $3.37\pm0.06^{bd}$ | $3.51\pm0.07^{ad}$ | $3.37\pm0.06^{bd}$ |
| **3.** | Induced and treated Piroxicam (2.5mg/kg) | $3.76\pm0.12^{bc}$ | $4.08\pm0.12^{ac}$ | $3.76\pm0.11^{bc}$ |
| **4.** | Induced and treated Carboplatin (2.5mg/kg) + Piroxicam (2.5mg/kg) | $2.67\pm0.08^{bd}$ | $3.59\pm0.48^{ad}$ | $2.67\pm0.08^{bd}$ |
| **5.** | Induced and treated Piroxicam (5mg/kg) | $1.87\pm0.47^{bd}$ | $2.59\pm0.89^{ad}$ | $1.87\pm0.46^{bd}$ |
| **6.** | Induced and treated Carboplatin (2.5mg/kg) | $2.78\pm0.30^{bd}$ | $3.92\pm0.07^{ad}$ | $2.78\pm0.30^{bd}$ |

Keys: a = significantly higher along the row ($p < 0.05$); b=significantly lower along the row ($p < 0.05$); c = significantly higher along the column ($p < 0.05$); d = significantly lower along the column ($p < 0.05$)

taglandin-dependent and independent cancer suppression potential of piroxicam [47], thereby reducing edema [48]. Substitution on the carboxamide nitrogen with a heteroanyl group gives piroxicam sevenfold more anti-inflammatory activity than the anyl group substitution [49]. Piroxicam (3.5 mg/kg) provided a longer therapeutic effect with a high safety margin [50], suggesting that hepatoma and lung adenomas caused by anthracene in animals [51] could be ameliorated by piroxicam. The most common lung tumors are carcinomas with the diameter size of ≤ 1 cm [52] and doubling time of 170 days [53] as observed in the group of rats (164.6 ± 5.5 days). The ability of carboplatin to ameliorate lung toxicity caused by anthracene disagrees with the report indicating that resistance has been developed against carboplatin [54]; modifications of functional groups of carboplatin at position 3 of the cyclobutane ring improve anticancer activity [55]. Moreso, the mechanism of action of carboplatin via platinum-adduct formation and that of piroxicam via cyclooxygenase enzyme inhibition suggest that a high dose of carboplatin is required to attack DNA; hence, carboplatin is highly tolerated [56], causing allodynia and cold hyperalgesia [57]. Therefore, carboplatin may be relatively safe, effective, and deliverable in the growing animals [58]. Induced carboplatin binding in phospholipid increased its anticancer activity [59].

**Carcinoembryonic antigen**

The carcino-embryonic antigen CEA is a diagnostic and prognostic tumor biomarker used for monitoring cancer initiation and progression [60]. Therefore, CEA is used for detection and staging of cancer. It is a glycoprotein biomarker used for monitoring gastrointestinal, colorectal, lung, and mammary tumors [61]. High CEA levels have been observed in epithelial tumors and 40–48% of non-small cell lung cancer, with higher sensitivity in advanced cancer [62, 63], suggesting that increased CEA in the present study may suggest lung tumor progression, connoting that numerous biomarkers are required for detection of lung tumors at an early stage [64].

**Effect of anthracene, carboplatin, and piroxicam on cardiorespiratory parameters of rats**

The decreased total oxygen consumption per kilogram, lung ventilation rate, and tidal volume, which are suggestive of dyspnea and hypoxemia observed in this study, agrees with the report that recommended oxygen for lung cancer patients [65]. However, oxygen use is not recommended for patients with advanced lung carcinoma [66], but adjuvant chemotherapy could cause linear peak oxygen consumption, as observed in the group administered carboplatin/piroxicam [67]. Tidal volume is a predictor of pulmonary complication in lung surgery [68]. Increased and decreased heart rate observed in the study agrees with the report of Franklin et al., which indicated that heart rate is a predictor of survival in non-small cell lung cancer and as such represents a therapeutic target as observed in the piroxicam-treated group [69]. Findings have shown that anthracene has very high potential to cause lung damage

**Table 6. Effects of anthracene and piroxicam on total oxygen consumption, oxygen consumption and heart rate of female rats**

| Group No. | Experimental Groups | Oxygen consumption ($mLh^{-1}$) | | | | |
|---|---|---|---|---|---|---|
| | | 0 | 7 | 21 | 35 | 42 |
| 1. | Induced not treated Water (2.5ml) | 286.8±32.4$^{bd}$ | 289.3±31.8$^{bd}$ | 312.8±30.4$^{ad}$ | 285.4±47.6$^{bd}$ | 289.3±46.1$^{bd}$ |
| 2. | Neither induced nor treated Water (2.5ml) | 280.7±34.8$^{bd}$ | 285.8±35.3$^{ad}$ | 281.0±38.1$^{bd}$ | 260.5±25.1$^{bd}$ | 266.7±22.1$^{bd}$ |
| 3. | Induced and treated Piroxicam (2.5mg/kg) | 283.2±20.4$^{bd}$ | 288.3±18.4$^{ad}$ | 282.7±37.4$^{bd}$ | 261.2±48.1$^{bd}$ | 262.4±49.3$^{bd}$ |
| 4. | Induced and treated Carboplatin (2.5mg/kg) + Piroxicam (2.5mg/kg) | 284.2±19.4$^{bd}$ | 289.5±19.4$^{bd}$ | 266.9±53.8$^{bd}$ | 297.8±74.1$^{bc}$ | 312.9±79.6$^{ac}$ |
| 5. | Induced and treated Piroxicam (5mg/kg) | 292.2±32.1$^{bc}$ | 296.2±31.7$^{bc}$ | 346.8±61.4$^{ac}$ | 285.1±41.7$^{bd}$ | 284.8±43.3$^{bd}$ |
| 6. | Induced and treated Carboplatin (2.5mg/kg) | 291.4±17.6$^{bd}$ | 294.8±18.1$^{ad}$ | 273.9±27.4$^{bd}$ | 263.8±32.5$^{bd}$ | 271.8±37.4$^{bd}$ |
| | | **Total oxygen consumption (mL/Kg/min)** | | | | |
| 1. | Induced not treated Water (2.5ml) | 20.00±0.00$^{ad}$ | 20.00±0.00$^{ad}$ | 20.00±0.00$^{ad}$ | 10.00±0.00$^{bd}$ | 10.00±0.00$^{bd}$ |
| 2. | Neither induced nor treated Water (2.5ml) | 10.00±0.00$^{bd}$ | 20.00±0.00$^{bd}$ | 20.00±0.00$^{bd}$ | 30.00±0.00$^{bc}$ | 30.00±0.00$^{ac}$ |
| 3. | Induced and treated Piroxicam (2.5mg/kg) | 40.00±0.00$^{ad}$ | 40.00±0.00$^{ad}$ | 20.00±0.00$^{bd}$ | 10.00±0.00$^{bd}$ | 10.00±0.00$^{bd}$ |
| 4. | Induced and treated Carboplatin (2.5mg/kg) + Piroxicam (2.5mg/kg) | 40.00±0.00$^{ad}$ | 40.00±0.00$^{ad}$ | 10.00±0.00$^{bd}$ | 10.00±0.00$^{bd}$ | 10.00±0.00$^{bd}$ |
| 5. | Induced and treated Piroxicam (5mg/kg) | 20.00±0.00$^{ad}$ | 20.00±0.00$^{ad}$ | 10.00±0.00$^{bd}$ | 10.00±0.00$^{bd}$ | 10.00±0.00$^{bd}$ |
| 6. | Induced and treated Carboplatin (2.5mg/kg) | 50.00±0.00$^{ac}$ | 50.00±0.00$^{ac}$ | 30.00±0.00$^{bc}$ | 20.00±0.00$^{bd}$ | 20.00±0.00$^{bd}$ |
| | | **Heart rate (beats/min)** | | | | |
| 1. | Induced not treated Water (2.5ml) | 840.58±4.06$^{bd}$ | 842.95±4.04$^{bd}$ | 865.26±3.97$^{ad}$ | 839.16±4.61$^{bd}$ | 842.95±4.56$^{bd}$ |
| 2. | Neither induced nor treated Water (2.5ml) | 834.60±4.16$^{bd}$ | 839.63±4.18$^{ad}$ | 834.85±4.28$^{bd}$ | 814.04±3.73$^{bd}$ | 820.46±3.57$^{bd}$ |
| 3. | Induced and treated Piroxicam (2.5mg/kg) | 837.01±3.48$^{bd}$ | 842.00±3.36$^{ad}$ | 836.54±4.26$^{bd}$ | 814.71±4.63$^{bd}$ | 815.95±4.67$^{bd}$ |
| 4. | Induced and treated Carboplatin (2.5mg/kg) + Piroxicam (2.5mg/kg) | 837.97±3.42$^{bd}$ | 843.17±3.42$^{bd}$ | 820.72±4.81$^{bd}$ | 851.17±5.35$^{bc}$ | 865.38±5.48$^{ac}$ |
| 5. | Induced and treated Piroxicam (5mg/kg) | 845.75±4.04$^{bc}$ | 849.67±4.03$^{bc}$ | 895.54±5.02$^{ac}$ | 838.87±4.42$^{bd}$ | 838.59±4.47$^{bd}$ |
| 6. | Induced and treated Carboplatin (2.5mg/kg) | 845.05±3.31$^{bd}$ | 848.28±3.34$^{ad}$ | 827.76±3.84$^{bd}$ | 817.50±4.06$^{bd}$ | 825.64±4.26$^{bd}$ |
| | | **Ventilation rate (liter $h^{-1}$)** | | | | |
| 1. | Induced not treated Water (2.5ml) | 848.65±95.94$^{bd}$ | 855.82±94.33$^{bd}$ | 925.60±90.01$^{ad}$ | 844.34±140.78$^{bd}$ | 855.82±136.21$^{bd}$ |
| 2. | Neither induced nor treated Water (2.5ml) | 830.65±103.23$^{bd}$ | 845.76±104.53$^{ad}$ | 831.38±112.81$^{bd}$ | 770.75±74.26$^{bd}$ | 789.15±65.26$^{bd}$ |
| 3. | Induced and treated Piroxicam (2.5mg/kg) | 837.76±60.24$^{bd}$ | 852.94±54.33$^{ad}$ | 836.44±110.69$^{bd}$ | 772.66±142.26$^{bd}$ | 776.21±145.91$^{bd}$ |
| 4. | Induced and treated Carboplatin (2.5mg/kg) + Piroxicam (2.5mg/kg) | 840.76±57.41$^{bd}$ | 856.50±57.52$^{bd}$ | 789.89±159.39$^{bd}$ | 881.12±219.23$^{bc}$ | 925.98±235.51$^{ac}$ |
| 5. | Induced and treated Piroxicam (5mg/kg) | 864.38±94.86$^{bc}$ | 876.45±93.79$^{bd}$ | 1026.22±181.79$^{ad}$ | 843.48±123.51$^{bd}$ | 842.62±128.06$^{bd}$ |
| 6. | Induced and treated Carboplatin (2.5mg/kg) | 862.24±52.27$^{bd}$ | 872.19±53.57$^{ad}$ | 810.38±81.13$^{bd}$ | 780.63±96.20$^{bd}$ | 804.17±110.69$^{bd}$ |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | **Lung volume (ml)** | | |
| **1.** | Induced not treated Water (2.5ml) | 10.30±0.53$^{bd}$ | 10.42±0.52$^{bd}$ | 11.59±0.48$^{ad}$ | 10.23±0.89$^{bd}$ | 10.42±0.86$^{bd}$ |
| **2.** | Neither induced nor treated Water (2.5ml) | 10.01±0.58$^{bd}$ | 10.26±0.59$^{ad}$ | 10.02±0.66$^{bd}$ | 9.04±0.37$^{bd}$ | 9.33±0.31$^{bd}$ |
| **3.** | Induced and treated Piroxicam (2.5mg/kg) | 10.13±0.28$^{bd}$ | 10.37±0.24$^{ad}$ | 10.10±0.64$^{bd}$ | 9.07±0.91$^{bd}$ | 9.13±0.94$^{bd}$ |
| **4.** | Induced and treated Carboplatin (2.5mg/kg) + Piroxicam (2.5mg/kg) | 10.17±0.26$^{bd}$ | 10.43±0.26$^{bd}$ | 9.35±1.06$^{bd}$ | 10.84±1.64$^{bc}$ | 11.60±1.80$^{ac}$ |
| **5.** | Induced and treated Piroxicam (5mg/kg) | 10.56±0.52$^{bc}$ | 10.76±0.51$^{bc}$ | 13.34±1.27$^{ac}$ | 10.22±0.75$^{bd}$ | 10.20±0.78$^{bd}$ |
| **6.** | Induced and treated Carboplatin (2.5mg/kg) | 10.53±0.23$^{bd}$ | 10.69±0.24$^{ad}$ | 9.67±0.42$^{bd}$ | 9.57±0.53$^{bd}$ | 9.57±0.65$^{bd}$ |
| | | | | **Tidal volume (mL)** | | |
| **1.** | Induced not treated Water (2.5ml) | 0.96±0.05$^{bd}$ | 0.99±0.05$^{bd}$ | 1.08±0.05$^{ad}$ | 0.96±0.08$^{bd}$ | 0.97±0.08$^{bd}$ |
| **2.** | Neither induced nor treated Water (2.5ml) | 0.94±0.06$^{bd}$ | 0.96±0.06$^{ad}$ | 0.94±0.06$^{bd}$ | 0.85±0.04$^{bd}$ | 0.87±0.03$^{bd}$ |
| **3.** | Induced and treated Piroxicam (2.5mg/kg) | 0.95±0.03$^{bd}$ | 0.97±0.02$^{bd}$ | 0.95±0.06$^{ad}$ | 0.85±0.08$^{bd}$ | 0.85±0.17$^{bd}$ |
| **4.** | Induced and treated Carboplatin (2.5mg/kg) + Piroxicam (2.5mg/kg) | 0.95±0.03$^{bd}$ | 0.97±0.03$^{bd}$ | 0.87±0.10$^{bd}$ | 1.01±0.15$^{bc}$ | 1.08±0.17$^{ac}$ |
| **5.** | Induced and treated Piroxicam (5mg/kg) | 0.98±0.05$^{bc}$ | 1.01±0.05$^{bc}$ | 1.25±0.12$^{ac}$ | 0.96±0.07$^{bd}$ | 0.95±0.07$^{bd}$ |
| **6.** | Induced and treated Carboplatin (2.5mg/kg) | 0.98±0.02$^{bd}$ | 1.00±0.02$^{ad}$ | 0.91±0.04$^{bd}$ | 0.86±0.05$^{bd}$ | 0.89±0.62$^{bd}$ |
| | | | | **Respiratory frequency (sec$^{-1}$)** | | |
| **1.** | Induced not treated Water (2.5ml) | 1.72±0.09$^{bd}$ | 1.76±0.09$^{bd}$ | 1.87±0.08$^{ad}$ | 1.03±0.09$^{bd}$ | 1.07±0.09$^{bd}$ |
| **2.** | Neither induced nor treated Water (2.5ml) | 1.56±0.09$^{bd}$ | 1.53±0.09$^{bd}$ | 1.38±0.09$^{bd}$ | 2.42±0.09$^{bc}$ | 2.87±0.09$^{ac}$ |
| **3.** | Induced and treated Piroxicam (2.5mg/kg) | 1.19±0.09$^{bd}$ | 1.67±0.09$^{ad}$ | 1.42±0.09$^{bd}$ | 1.02±0.09$^{bd}$ | 0.98±0.09$^{bd}$ |
| **4.** | Induced and treated Carboplatin (2.5mg/kg) + Piroxicam (2.5mg/kg) | 1.41±0.09$^{ad}$ | 1.40±0.09$^{bd}$ | 0.87±0.09$^{bd}$ | 0.57±0.09$^{bd}$ | 0.52±0.09$^{bd}$ |
| **5.** | Induced and treated Piroxicam (5mg/kg) | 1.74±0.09$^{bd}$ | 1.77±0.09$^{ad}$ | 0.73±0.09$^{bd}$ | 1.23±0.09$^{bd}$ | 1.17±0.09$^{bd}$ |
| **6.** | Induced and treated Carboplatin (2.5mg/kg) | 1.86±0.09$^{ac}$ | 1.74±0.09$^{bc}$ | 2.15±0.10$^{bc}$ | 1.71±0.11$^{bd}$ | 1.42±0.10$^{bd}$ |

Keys: a = significantly higher along the row ($p < 0.05$); b = significantly lower along the row ($p < 0.05$); c = significantly higher along the column ($p < 0.05$); d = significantly lower along the column ($p < 0.05$); total volume = 0.6–1.5ml; respiratory frequency= 1.17–2.5 breaths per second; lung volume = 6–12ml

despite the fact that the US Environmental Protection Agency has indicated that not enough information exists to classify anthracene as a cancer-causing substance [70].

## CONCLUSION

Anthracene exposure in female rats resulted in reduced body and organ weights, altered lung morphology, and impaired cardiorespiratory function. Treatment with piroxicam and carboplatin ameliorated these effects in a dose-dependent manner. Carboplatin treatment completely resolved micronodular lung lesions, while piroxicam reduced their size, suggesting a potential synergistic benefit of combined therapy. These findings indicate that piroxicam, alone or in combination with carboplatin, may have therapeutic potential in managing anthracene-induced lung tumorigenesis.

### Ethical Statement

All experimental procedures involving animals were conducted in accordance with the guidelines of the Animal Ethics Committee of the College of Veterinary Medicine, Joseph Sarwuan Tarka University, Makurdi, Nigeria (Permit No. JOSTUM/CVM/ETHICS/2025/07).

### Conflict of Interest

The authors have no conflict of interest to disclose.

### Data Availability Statement

The raw data of this article will be made available by the authors, without undue reservation.


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### Authors' Contributions

SAS designed the study and analyzed the data. AMU carried out the study and collected the data. SAS, AMU, AMV and TA wrote, proofread and approved the manuscript.

### Generative AI Statement

No generative artificial intelligence (AI) and AI-assisted technologies were used in writing the manuscript.


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