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Nutraceutical potential of Rosmarinic acid on formaldehyde-induced lung toxicity in Wistar rat: A dose response study

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Abstract

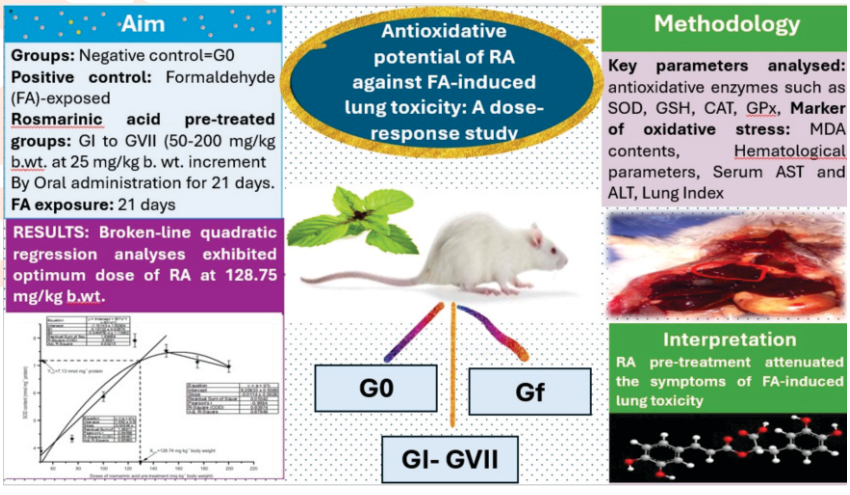
Aim: To evaluate the anti-oxidative potential of Rosmarinic acid, one of the most abundant active components of basil leaves, against formaldehyde induced lung toxicity in male Wistar rats.

Methodology: Experimental animals (150±3.3 g) were divided into nine groups (n=6 animals/groups). Animals of first group served as control (G_0), second group were formaldehyde treated (G_f), third group animals were pre-treated with different doses of rosmarinic acid ranging 50 to 200 mg kg^{-1} b.wt. at increment of 25 mg kg^{-1} b.wt. Rosmarinic acid was administered oral for 21 days and pre-treated groups were then exposed to formaldehyde for 21 days.

Results: Increasing doses of rosmarinic acid pre-treatment up to 125 mg kg^{-1} b.wt. had a significant influence on the antioxidative enzymes, hematological parameters, serum biochemistry and lung index. To establish best dose with high efficacy, superoxide dismutase (SOD) data was subjected to quadratic-broken-line regression analyses which exhibited best dose of 128.75 mg kg^{-1} b.wt rosmarinic acid to reverse lung toxicity.

Interpretation: These findings indicate that rosmarinic acid has the potential to inhibit formaldehyde-induced lung injury through inhibition of oxidative stress and hypersensitivity.

Key words: Formaldehyde, Lung toxicity, Nutraceutical, Rosmarinic acid, Serum biochemistry



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Introduction

The lower respiratory tract is one of the prone area for most allergies, pollutants, toxicants, and infections, including bacteria and viruses. The organisms find their way into the distal airway, grow in or on the epithelium, resulting in inflammation, increased mucus output, and compromised mucociliary health. In severe cases, inflammation and epithelial necrosis may choke small alveoli, blocking airways, thereby causing congestion. Numerous other essential organs are also affected due to reduced oxygen flow into the lungs in chronic situations, which may result in multi-organ failure. One of the most prevalent aldehydes in the environment is formaldehyde, which has been linked to respiratory illnesses as a necessary indoor irritant (Bhat *et al.,* 2024; Enya *et al.,* 2025). All individuals who work closely with formaldehyde, including painters, anatomists, histology technicians, and students studying biology and the life sciences, are aware of its toxic nature (Celik *et al.,* 2001; Frigas *et al.,* 1984). Formaldehyde's primarily target is the respiratory system. Regular inhalation of greater quantities of formaldehyde results in inflammation and asthma. Cui *et al.* (1996), observed that the volume of formaldehyde was greater in the lungs than in other organs after rats inhaled it.

Plants have long been utilized as medicines in therapies, immune system boosters, and preventative measures. An estimated 80% of the world's population currently uses herbal treatments to cure various illness (Ogbera *et al.,* 2010). Basil, or sweet basil (*Ocimum basilicum*) is a medicinal plant that belongs to family Labiatae. The leaf extract of basil leaves extracts have potent antioxidant, anti-aging, anticancer, antiviral, and antimicrobial properties (Chiang *et al.,* 2005, Eid *et al.,* 2023, Güez *et al.,* 2017, Romano *et al.,* 2022, Nadeem *et al.,* 2022, Ahmed *et al.,* 2019). In most countries, including the Kingdom of Saudi Arabia, the herb is widely available. Farasan is a beautiful Island situated near Jazan in Kingdom of Saudi Arabia. With its unique natural elements and rich biodiversity, it has recently been registered under the UNESCO's Man and Biosphere's list. This herb is found planted outside the houses in many of the local population and is locally known as Rayha'n. People like it probably due to its aroma.

Rosmarinic acid is one of the most prevalent and important phenolic compounds constituting 15.74% sweet basil (*O. basilicum*). Because of its intriguing biological activities and diverse pharmacological characteristics, including antiviral, antibacterial, anti-inflammatory, and antioxidant actions, it qualifies as a nutraceutical compound. Since it mitigates the effects of reactive oxygen species that are produced in the body in response to stress it is becoming a crucial part of both human and animal nutrition. Studies have further confirmed the potential of Rosmarinic acid to work as an anti-microbial, immunomodulatory, anti-diabetic, anti-allergic, anti-inflammatory, hepato- and renal-protectant agent, beneficial effects during skin diseases, lung adenocarcinoma (Alagawany *et al.,* 2017; Ahmed *et al*., 2021). Lung epithelial cells are a primary target for ROS. The generation of ROS and are exposed to different stressors is increased in conditions such as inflammation, or exposure to air pollutants and cigarette smoke. ROS and their reactions with lung epithelial cells participate in the pathophysiology of several lung diseases. Lungs and blood have enzymatic antioxidants such as superoxide dismutase (SOD) and catalase (CAT), and all play an important role in oxidant toxicity (Eftekhara *et al.,* 2018, Hadwan *et al.,* 2024). High intracellular and extracellular levels of antioxidants protect lung epithelial cells. Malondialdehyde (MDA) is a potential indicator of some health-related acute problems including lung disease. Furthermore, malonaldehyde (MDA) is a well-recognized marker of lipid peroxidation (LPO) and hence oxidative stress. The role of MDA on normal tissues has been widely investigated. The present study was, therefore, conducted to explore the nutraceutical potential and protective effect of Rosmarinic acid on the respiratory health of Wistar rats exposed to formaldehyde in Rosmarinic acid pre-treated groups.

Materials and Methods

Ethical Aspects and approval: The present study was conducted in accordance with the Ethical Guidelines of the University to ensure that use of animals does not infringe any provision of animal ethics. Efforts were made to minimize the suffering of rats during experimental procedures. All the protocols used in the present study have been approved by the Animal Ethical Committee registered under R.No. 801/Go/RE/S/2003/ CPCSEA (Faculty of Life Sciences, Department of Zoology, Sher-e-Kashmir University, J&K, India). Further, this study fully complies with the UK Guidelines on the operation of the Animals (Scientific Procedures) Act 1986, the EU Directive 2010/63, and the NIH Guide for the Care and Use of Laboratory Animals. Further it was ensured that the reporting aligned with the Guidelines of Animal Research: Reporting of *In Vivo* Experiments.

Experimental Animals: Male albino Wistar rats weighing 150±3.3 g were housed in standard polypropylene cages with six rats per cage (n=6), under standard laboratory conditions with a constant temperature of 25±1.8°C and a relative humidity of 50±10%. The rats were given free access to food and water and kept in a 12 hr light/dark cycle. Rosmarinic acid (≥98% (HPLC, Sigma Aldrich St. Louis, MO, USA) was orally administered once a day for 21 days @ 50-200 mg kg^{-1} b.wt. with the help of an intragastric tube. All the animals were weighed every week.

Experimental design: Lung toxicity was induced by exposing the test animals to 40% formaldehyde by soaking cotton wool in formaldehyde and placed in enclosed (designed) wire gauze within the animal cage, exposing the animals to formaldehyde vapor for 21 days. Male albino Wistar rats were randomly divided into nine groups: G_0 negative control groups where animals were neither exposed to formaldehyde nor pretreated with Rosmarinic acid; G_f animals of positive control groups devoid of rosmarinic and pretreatment and exposed to formaldehyde only for 21 days G_t: animals of rosmarinic acid (≥98% (HPLC, Sigma Aldrich, St. Louis, MO, USA) pre-treated groups treated with rosmarinic acid

at 50 mg kg^{-1} b.wt. (G_I), 75 mg kg^{-1} b.wt. (G_{II}), 100 mg kg^{-1} b.wt. (G_{III}), 125 mg kg^{-1} b.wt. (G_{IV}), 150 mg kg^{-1} (G_V), 175 mg kg^{-1} b.wt. (G_{VI}) and 200 mg rosmarinic acid kg^{-1} b.wt. (G_{VII}) which were then exposed to 40% formaldehyde for 21 days. All rats were weighed before and at the end of the experiments under prior fasting of 24 hr and change in the body weight if any was determined. At the end of the experiment, the rats were sacrificed and lungs were immediately removed from carcass, washed in a cold buffer to remove traces of red blood cells, blotted on filter paper and weighed to determine the lung index.

Calculations of lung indices and percent survival: In order to assess the effects of rosmarinic acid pre-treatment on formaldehyde induced-lung toxicity the following parameters were evaluated: Lung index was determined by dividing the lung weight (g) by final body weight (g) and multiplying by 100. Survival Rate was determined by dividing the Final number of rats by Initial number of rats and multiplying by 100.

Estimation of water content in lung tissue: The animals were dissected to take out the lungs, thereafter, the surface blood in the lungs was dried using an absorbent strip, weighed immediately, and kept at 60°C in a hot air oven for 72 hr, until no further weight reduction was observed. Subsequently, the dry weight of the lung tissue was calculated and the water content (%) in the lung tissue was determined.

Collection of blood and serum: Animals were sacrificed by decapitation under humane conditions after overnight fasting at the termination of 21-days experiment. Heart punctures were used to obtain the blood samples, which were then placed in an anticoagulant-free tubes and centrifuged for 15 min at 3000 rpm. The resulting serum was refrigerated for further examination. Concurrently, a sandwich ELISA kit (CUSABIO Technology LLC, Houston, TX 77054, United States) was used to measure the total IgE levels (ng ml^{-1}). A tissue homogenizer was used to homogenize the lung tissue in 0.1 M cold phosphate buffered saline (PBS; pH -7.4). For homogenization, a dilution of 1:10 (w/v) was employed. The homogenate was centrifuged at 10,000 g for 20 min (REMI, Maharashtra, India) at 4°C, and the supernatant was obtained which was used for assessment of the antioxidative enzyme activities and oxidative stress indicators.

SOD and MDA levels were detected in the lung tissue of rats using assay kits from Boster Biological Technology, Ltd., in strict accordance with the manufacturer's protocol. According to Aebi (1984), the catalase activity was calculated by the rate of H_2O_2 decomposition. The specific activity of catalase was measured in mg enzymatically produced protein, or units of CAT. Reduced glutathione activity was estimated following the method of Ellman (1959). The homogenate was centrifuged after adding 10% TCA, 2.0 m phosphate buffer pH 8.0 and Ellman's reagent in 100 ml of 0.1% $NaNO_3$ to 1.0 ml of supernatant. The reaction mixture was vortexed spectrophotometrically (Genesys, Germany) and the absorbance was read at 412 nm. The homogenate was centrifuged after adding 10% trichloroacetic acid (TCA). 3.0 ml of phosphate buffer (0.2 M, pH 8.0) and 0.5 ml of Ellman's reagent (19.8 mg of 5,5-dithiobis nitrobenzoic acid (DTNB) in 100 ml of 0.1% sodium nitrate) were added to 1.0 ml of supernatant. The mixture was vortexed spectrophotometrically (Genesys, Germany) and the absorbance was at 412 nm. Complete blood counts were done as per the standard protocol using commercial kits. Using an automatic analyzer (Vet Scan VS2, Abaxis, Union City, CA), the aspartate aminotransferase and alanine aminotransferase activities in the serum were measured in accordance with the manufacturer's instructions. The unit of enzyme activity was IU/L.

Statistical analysis: The experimental data were subjected to One-way ANOVA (Sokal 2003). Optimum dose of Rosmarinic acid was determined according to the method of Baker *et al.* (2022) and Parr (2003) in which the broken-line and quadratic analyses were superimposed and the optimum dose was determined by establishing the point where the quadratic curve first intersected the plateau of broken-line. Differences among the treatment means were determined by Tukey's significant difference test at a $P<0.05$ level of significance (Tukey, 1953). Statistical analysis was done using Origin Software, version 8.1 San Clemente, CA. The experiment were conducted in quadruplicates (n=4).

Results and Discussion

Pretreatment with rosmarinic acid had protective effects on lungs of animals exposed to formaldehyde for 21-days. No dead rat was observed during the 21-days trial. The body weight was significantly lower for the groups pre-treated with Rosmarinic acid at 50 and 75 mg kg^{-1} b.wt. and these pre-treated groups exhibited lethargy, which may probably be in response to adverse physiologic conditions, due to lung damage. However, the rats of negative control group remained healthy and active throughout the study period. Table 1 shows the change of body weight during the 21 days of experiment. The formaldehyde-treated positive control group rats (G_f) had significant reduction in the mean body weight (average body weight 132.3 ± 2.3 g; $P<0.05$) compared to the negative control group animals (G_0; weight 151± 1.4 g). Groups G_I, G_{II} and G_{III} rats administered with Rosmarinic acid at 50, 75 and 100 mg kg^{-1} b.wt. could not tolerate the toxic effects of formaldehyde exposure, their weight was reduced significantly compared to the groups receiving pretreatment at higher doses of RA at 100, 125 mg kg^{-1} and 150 mg kg^{-1} body weight where a significant increase in weight gain ($P<0.05$) of groups G_{III}, G_{IV} and G_V animals was recorded. However, no gain in weight was recorded for Groups G_{VI} (150.7 ±1.2 g) and Group G_{VII} (149.4±1.3 g) animals administrated with higher doses of Rosmarinic acid.

Lung index and Water content: The lung index (LI) and wet weight and water content of the lungs significantly increased ($P<0.05$) for the positive control groups (G_f) and the animals of the groups who received Rosmarinic acid pretreatment at lower doses in G_I and G_{II} groups, respectively. However, L_I and edema were improved in G_{III} group animals and restored to their normal values in animals of Groups G_{IV}-G_{VII} animals (Table 1). SOD, CAT

Table 1: Body weight, water content of lung and % survival of Rosmarinic acid pre-treated Formaldehyde exposed animals

			Rosmarinic acid + Formaldehyde groups						
Parameters	**Normal control (G_0)**	**Formaldehyde treated control (G_f)**	**50 mg kg^{-1} body weight (G_I)**	**75 mg kg^{-1} body weight (G_{II})**	**100 mg kg^{-1} body weight (G_{III})**	**125 mg kg^{-1} body weight (G_{IV})**	**150 mg kg^{-1} body weight (G_V)**	**175 mg kg^{-1} body weight (G_{VI})**	**200 mg kg^{-1} body weight (G_{VII})**
Initial weight (g)	150±2.1^a	150.3±1.5^a	149.1±2.3^b	150.4±1.5^a	150.2±2.1^a	150.4±1.1^a	150.7±1.2^a	150.1±1.3^a	150.5±1.4^a
Final weight (g)	151.1±1.4^a	132.3±2.3^f	135.1±1.7^e	139.9±1.5^d	146.8±1.2^c	149.7±1.3^b	150.2±1.7^a	150.7±1.2^a	149.4±1.3^b
Lung index (%)	0.99±0.01^d	1.44±0.03^a	1.26±0.01^b	1.21±0.04^b	1.06±0.01^c	1.05±0.02^c	1.06±0.01^c	1.05±0.03^c	1.07±0.01^c
Water content of the Lung (%)	80.9±0.5^f	89.3±0.3^a	87.4±1.1^b	84.5±0.7^c	81.7±1.3^d	79.9±0.7^e	80.1±0.9^e	81.5±1.2^d	81.9±1.5^d
Survival Rate (SR %)	100^a	100^a	100^a	100^a	100^a	100^a	100^a	100^a	100^a

and GSH activities showed a substantial (P<0.05) decrease in G_f group rats (Table 2). Formaldehyde inhalation caused a significant decrease in CAT (2.79 nmol H_2O_2 decomposed min mg^{-1} protein) and (GSH 12.97 nmol mg^{-1} protein) activities in lung tissue of G_f groups as compared to G_0 group rats. However, the groups G_I, G_{II}, G_{III} and G_{IV} exhibited gradual improvement in these antioxidative enzymes in lung tissue. For the groups G_{VI} and G_{VII}, however, these values remained essentially unchanged (P>0.05, Table 2). The lipid peroxidation level in terms of MDH content, in the lung tissues significantly increased (P<0.05) in formaldehyde-challenged rats compared to negative control groups. Pre-treatment of FA exposed groups (Gf) with Rosmarinic acid at 125 mg kg^{-1} showed a significant (P<0.05) decrease in MDA content in comparison to G_f and other group animals. Rosmarinic acid given @ 125 mg kg^{-1} in Group G_V showed maximum decrease in MDA content of lung tissue

The total serum IgE level was statistically higher in G_f group rats as compared to other groups. Furthermore, compared to the negative control group, RA pre-treated FA inhaled animals with low levels of RA pretreatment at 50 and 75 mg kg^{-1} b.wt. markedly raised the serum IgE level. When compared to the negative control group, high level of RA pre-treatment in FA-inhaled rats resulted in a negligible rise in serum IgE (P<0.05, Table 2). G_f group rats exhibited increase in the number of white blood cells and a significant decrease in the red blood cells and heamoglobin levels. However, significant improvements in the haematological profiles were recorded for the Rosmarinic acid pre-treated formaldehyde exposed groups, and the RBCs, Hb and heamatocrit levels in G_{IV} groups rats significantly improved. However, G_V, G_{VI} and G_{VII} group animals showed no further improvement in these parameters. Similarly, erythrocyte Osmotic Fragility (EOF) in terms of percent haemolysis showed significant decrease (P<0.05) from diet G_I to G_{IV}. GIV group animals exhibited lower susceptibility to haemolysis when placed in a hypotonic salt solution indicating that erythrocytes were more resistant to haemolysis. However, the G_V, G_{VI} and G_{VII} groups did not exhibit any further improvement in EOF (P>0.05) in hypotonic salt solution (Table 3). Serum AST and ALT in G_f group rats showed a significant increase of 80% and 24.24% as compared with the negative control groups (Table 3). The AST levels exhibited statistically significant (P<0.05) increase in the formaldehyde exposed pre-treated groups. The AST activities also restored to its normal physiological values (26 IU/L) in G_{IV} group rats. The corresponding ALT levels showed almost similar trend. The adverse effects of formaldehyde inhalation on these serum biomarkers were insignificant in a dose-dependent manner in G_V, G_{VI} and G_{VII} groups.

To generate precise information on best dose of rosmarinic pre-treatment, the experimental data of super oxide dismutase were subjected to quadratic-broken-line regression analyses. The two models were superimposed in order to determine the ideal rosmarinic pre-treatment dose, the point at which the quadratic curve first crossed the broken-line plateau was identified, and the average value was computed. The ideal rosmarinic pre-treatment dose to control formaldehyde induced lung toxicity was 128.74 mg kg^{-1} b.wt. by the abscissa of junction of the straight broken-line with a quadratic regression curve (Fig. 1). The formaldehyde-induced lung damage in male rats were significantly reduced in G_{IV} group rats indicating that Rosmarinic acid, may have an ameliorative effect on the lung epithelium by reversing the physiological changes brought by formaldehyde due to strong antioxidative action. The health-promoting benefits of rosmarinic can be linked to the scavenging reactive oxidation species, decreasing nitric oxide production, lipid peroxidation, increasing high-density lipoprotein, decreasing low-density lipoprotein levels, and deranged hemolysis (Baba *et al.,* 2005; Guo *et al.,* 2020).

Formaldehyde-treated positive control group rats (Gf) had significant reduction in the mean body weight (average body weight 132 ± 8 g; P< 0.05). The findings of this study are in line with previous studies where a decline in body weight in response to formaldehyde exposure has been reported. A decrease in the body weight at ≥ 10% of control values were also observed in formaldehyde-exposed male rats at 2 ppm for 6 hours, 5 days/week for 28 months (Kamata *et al.,* 1977), developing

Table 2: Markers of antioxidative enzymes and oxidative stress in lung homogenate of Rosmarinic acid pre-treated Formaldehyde exposed animals

			Rosmarinic acid + Formaldehyde groups						
Parameters	**Normal (Negative) control (G_0)**	**Formaldehyde treated (positive control) (G_f)**	**50 mg kg^{-1} body weight (G_I)**	**75 mg kg^{-1} body weight (G_{II})**	**100 mg kg^{-1} body weight (G_{III})**	**125 mg kg^{-1} body weight (G_{IV})**	**150 mg kg^{-1} body weight (G_V)**	**175 mg kg^{-1} body weight (G_{VI})**	**200 mg kg^{-1} body weight (G_{VII})**
IgE (ng ml^{-1})	31.25±2.31^{g}	79.11±5.83^{a}	67.89±3.61^{b}	64.97±7.05^{c}	51.14±2.39^{d}	39.54±4.44^{f}	41.15±5.19^{e}	41.58±2.42^{e}	41.94±2.97^{e}
GSH (nmol mg^{-1} protein)	22.23±2.11^{a}	12.97±1.15^{g}	15.77±1.43^{f}	16.54±1.94^{e}	17.97±2.13^{d}	20.21±1.31^{b}	19.89±1.21^{c}	19.16±1.18^{c}	19.07±1.51^{c}
CAT (nmol of H_2O_2 decomposed min mg^{-1} protein)	6.97±1.12^{a}	2.79±0.98^{e}	3.87±0.87^{d}	4.21±0.65^{c}	5.14±0.59^{b}	5.89±0.93^{b}	5.47±0.51^{b}	4.98±0.74^{c}	4.91±0.91^{c}
SOD (nmol mg^{-1} protein)	8.67±0.05^{a}	2.41±0.09^{g}	3.89±0.07^{f}	4.34±0.81^{e}	5.87±0.14^{d}	7.91±0.15^{b}	7.54±0.45^{b}	7.13±0.71^{b}	6.97±0.41^{c}
MDA (nmol mg^{-1} protein)	4.34±1.17^{f}	15.11±1.15^{a}	11.33±1.14^{b}	10.56±1.13^{b}	9.14±1.34^{c}	7.11±1.23^{e}	7.41±1.31^{e}	8.11±1.01^{d}	7.91±0.09^{e}

female rats exposed to 6 ppm, 8 hours/day for 6 weeks (Kum *et al.,* 2007), male rats exposed to 9.9 or 19.9 ppm, 8 hours/day, 5 days/week for 4 or 13 weeks (Ozen *et al.,* 2002), male rats exposed to 5 or 10 ppm, 8 hours/day, 5 days/week for 4 or 13 weeks (Oğuz *et al.,* 2003), and female mice exposed to 5 or 10 ppm, 6 hours/day, 5 days/week for 2 weeks (Woon-Won *et al.,* 2007). Lungs represent the first frontier between oxygen entry into the organism and delivery to the mitochondria and are therefore exposed to higher concentrations of oxygen and reactive oxygen species (Ward 2010), leading to the amplification of inflammatory processes (Zimmerman, 2001). A disruption of oxidative balance was found to be important in the pathogenesis of lung (Crimi *et al.,* 2006; Rahman *et al.,* 2003).

The most recognized predicative markers for body's antioxidant system and oxidative stress are superoxide dismutase (SOD), catalase (CAT), glutathione (GSH) and malonaldehyde (Al-Abrash *et al.,* 2000; Nandi *et al.,* 2019). Hydrogen peroxide (H_2O_2) is one of the main reactive oxygen species leading to oxidative stress. It is continuously generated by several enzymes including superoxide dismutase and must be degraded to prevent oxidative damage. The cytotoxic effect of H_2O_2 is thought to be caused by hydroxyl radicals generated from iron-catalyzed reactions, causing subsequent damage to DNA, proteins, and membrane lipids. Glutathione and catalase are the two main enzymes involved in H_2O_2 detoxification. MDA is a product of lipid peroxidation and the most representative indicator of extent of oxidative stress in the body (Al-Abrash *et al.,* 2000; Nandi *et al.,* 2019).

Formaldehyde-treated positive control animals showed a significantly lower levels of serum superoxide dismutase (SOD), Catalase (CAT) and glutathione (GSH) and higher MDA values indicating formaldehyde induced toxicity. Higher MDA contents in G_f group rats could be due to inhalation of formaldehyde that might have resulted in significant generation of free radicals leading to MDA formation. Significant improvement in these markers were exhibited in a dose-dependent manner in RA pre-treated groups. Rosmarinic acid pre-treatment of animals of G_{IV} group significantly reverted the biochemical changes induced by formaldehyde-exposure and also restored the levels of antioxidant enzymes and MDA content to almost normal physiological values ($P<0.05$). A significant decrease in the MDA content ($P<0.05$) was recorded in G_{IV} group rate, which might be due to the anti-oxidative and anti-inflammatory effects of rosmarinic acid. Rosmarinic acid also exhibited protective action against Malathione (pesticide) induced lung damage through anti-inflammatory, antioxidant, and anti-apoptotic functions in albino Wistar rat models (Ahmed *et al.,* 2021).

These findings are in line with previous studies which have reported the anti-inflammatory, antioxidant, and anti-apoptotic potential of rosmarinic acid on lung tissues against the toxic effects of Malathione (Ahmed *et al*., 2021), and that the RA treatment delays development of drug resistance in cases of lung adenocarcinoma (Yuan *et al*., 2024, Harindranath *et al*., 2025, Li *et al*., 2025, Zhou *et al*., 2025). Studies have also reported that exposure to formaldehyde poses deleterious effects on the respiratory system, which may lead to a variety of negative outcomes including immune system dysregulation and oxidative stress, both of which worsen inflammatory processes and cause tissue damage (Lu *et al*., 2022, Bhat *et al.,* 2024). Haematological profiles provide valuable information on the organism's internal environment (Kum *et al.,* 2007). Outcome of the present study clearly indicate that formaldehyde inhalation had a significant impact on the rats' haematology. The decrease in the red blood cell contents could likely be the result of harmful effects of formaldehyde on bone marrow or direct destruction of erythrocytes. The information gathered suggested a potential case of macrocytic hypochromic anemia, were formaldehyde

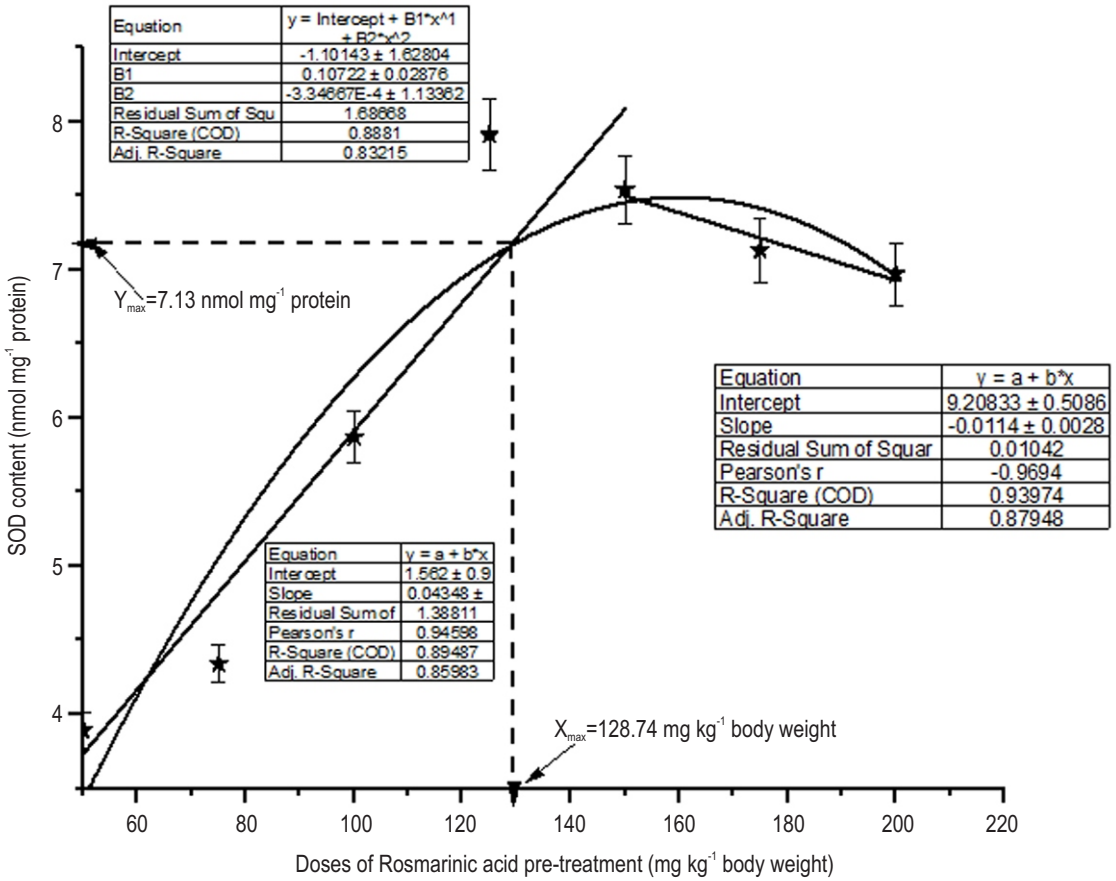

Fig. 1: Broken-line quadratic regression analyses of doses vs SOD values in lung homogenate.

inhalation in positive control groups increased the reactive oxygen species that might have led to erythrocyte destruction by negatively affecting the erythrocyte membranes which might have led to a decrease in the red blood cell life span resulting macrocytic hypochromic anemia. Formaldehyde inhalation in rosmarinic acid pre-treated groups significantly ameliorated these negative effects on the hematological metrics in an incremental manner with the best values obtained in G_{IV} group rats. Incremental levels of Rosmarinic acid had a declining trend in leucocyte contents of the animals, showing a dose-dependent effect. Erythrocytes breakdown was reported to be faster in case of improper membrane function (Kim-Shapiro *et al.,* 2011).

In this study, FA exposed G_f groups had significantly high erythrocyte membranes lysis. Erythrocyte osmotic fragility in terms of percent haemolysis was found to decrease significantly ($P<0.05$) in G_I to G_{IV} group rats, which might be due to the fact that cell wall strength was probably restored with rosmarinic acid pre-treatment at 125 mg kg^{-1} b.wt. (Table 3). The changes in AST and ALT levels serve as an indicator of liver damage or injury (Goorden *et al.,* 2013) and when liver cells are damaged or undergo necrosis, these enzymes are released into the bloodstream, resulting in increased levels of AST and ALT in the blood (Pastori *et al.,* 2022). At the end of experiment, *i.e.,* 4th week, G_I group rats had significantly higher concentrations of serum AST and ALT and IgE ($P<0.05$), which could be due to oxidative damage that the liver tissue sustained from formaldehyde in inhalation animals of G_f group. These findings are in line with those of Ebojele *et al.* (2021, 2023) who observed a significant rise in the serum AST and ALT activities. Furthermore, the hepatic enzymes and total IgE showed a declining trend among the groups pre-treated with rising levels of rosmarinic acid up to 125 mg kg^{-1} b.wt. and then exposed to formaldehyde inhalation. However, no further improvement was recorded in the groups rosmarinic acid pretreated and formaldehyde exposed groups receiving pre-treatment of rosmarinic acid at still higher levels at 150 (G_V), 175 (G_{VI}) and 200 (G_{VII}) mg kg^{-1} b.wt.

Several studies in the past have suggested that chemical toxicant if inhaled or ingested causes respiratory problems such as pulmonary edema, *i.e.,* accumulation of fluid in the lungs. Studies have found that rosmarinic acid exhibits strong antioxidant activity in the biological systems by scavenging free radical and reactive oxygen species (Noor *et al.,* 2022, Kim *et al.,*

Table 3: Hematological parameters and serum biochemistry of Rosmarinic acid pre-treated Formaldehyde exposed animals

			Rosmarinic acid + Formaldehyde groups						
Parameters	**Negative control (G_0)**	**Formaldehyde treated control (G_f)**	**50 mg kg^{-1} body weight (G_I)**	**75 mg kg^{-1} body weight (G_{II})**	**100 mg kg^{-1} body weight (G_{III})**	**125 mg kg^{-1} body weight (G_{IV})**	**150 mg kg^{-1} body weight (G_V)**	**175 mg kg^{-1} body weight (G_{VI})**	**200 mg kg^{-1} body weight (G_{VII})**
Hb (g dl^{-1})	13.1±0.2^{a}	9.9±0.5^{e}	10.1±0.3^{d}	10.8±0.5^{d}	11.5±0.4^{c}	12.1±0.7^{b}	11.9±0.5^{c}	11.7±0.3^{c}	11.4±0.6^{c}
RBC count	3.85±0.31^{a}	2.92±0.38^{e}	2.91±0.14^{e}	3.15±0.73^{f}	3.74±0.81^{c}	3.95±0.13^{b}	3.58±0.13^{d}	3.53±0.44^{d}	3.49±0.43^{e}
Packed cell volume %	42.2±0.4^{a}	27.8±0.3^{g}	30.2±0.7^{f}	34.3±0.5^{e}	37.1±0.4^{d}	39.9±0.8^{b}	38.5±0.9^{c}	37.7±0.4^{d}	37.1±0.3^{d}
ESR (Westergen) mm hr^{-1}	19±2^{g}	73±3^{a}	64±1^{b}	57±2^{c}	32±5^{d}	24±3^{e}	29±4^{f}	33±5^{d}	34±4^{d}
EOF (% hemolysis)	39.7±0.2^{g}	78.5±0.4^{a}	65.2±0.7^{b}	51.9±0.9^{c}	44.7±0.7^{d}	41.5±0.4^{f}	41.1±0.7^{f}	40.5±0.5^{e}	40.9±0.5^{e}
Differential Cell Count									
Neutrophils (%)	69.9±0.5^{h}	90.6±0.7^{a}	87.3±0.7^{b}	83.9±0.1^{c}	75.9±0.1^{f}	69.6±0.3^{h}	74.1±0.1^{g}	78.7±0.4^{e}	79.5±0.5^{d}
Lymphocyte (%)	32.3±0.1^{h}	57.8±0.1^{a}	55.1±0.3^{b}	43.4±0.3^{c}	41.7±0.2^{d}	32.9±0.1^{h}	34.4±0.3^{g}	36.3±0.3^{f}	37.4±0.7^{e}
Monocytes (%)	7.1±0.9^{e}	11.9±0.5^{a}	11.3±0.1^{a}	10.1±0.5^{b}	8.8±0.7^{d}	7.5±0.5^{e}	8.1±0.4^{d}	9.5±0.5^{c}	9.1±0.2^{c}
Eosinoils (%)	1.8±0.3^{f}	4.5±0.1^{a}	3.8±0.7^{b}	2.9±0.7^{c}	2.5±0.1^{d}	1.9±0.3^{e}	2.1±0.5^{e}	2.4±0.7^{d}	2.7±0.1^{c}
Basophils	0.5±0.7^{f}	3.1±0.3^{a}	2.4±0.5^{b}	1.9±0.1^{d}	1.1±0.4^{e}	0.6±0.1^{f}	1.1±0.3^{e}	1.1±0.6^{e}	1.2±0.5^{c}
AST (IU l^{-1})	25±3^{h}	45±2^{a}	41±3^{b}	37±5^{c}	31±4^{d}	26±5^{e}	27±2^{ef}	28±4^{f}	29±3^{fg}
ALT (IU l^{-1})	33±1^{e}	41±2^{a}	39±3^{b}	37±5^{c}	35±2^{d}	32±4^{e}	34±3^{d}	37±4^{c}	38±2^{c}

2020). Recently, Sadeghi *et al.* (2020) investigated the impact of rosmarinic acid on lipopolysaccharide-induced oxidative damage and inflammation in peripheral blood mononuclear cells. The study demonstrated rosmarinic acid-mediated reduction in lipid peroxidation levels and restored antioxidant balance. According to Sanbongi *et al.* (2017), rosmarinic acid also prevents lung damage caused by diesel exhaust particles by lowering the expression of proinflammatory molecules. Stansbury (2014) elucidated the role of rosmarinic acid as a novel agent in the treatment of allergies and asthma, due to free radical scavenging ability and suppression of allergic immunoglobulin and inflammatory responses of polymorphonuclear leukocytes, which may underline its efficacy in the treatment of allergic disorders, as demonstrated in clinical trials. It is a valuable agent for treating allergic conditions, which is of importance considering the recent increase in the incidence of allergies, asthma and lung diseases associated with airborne pollutants. The findings of this study will be of high therapeutic significance to boost the immunity of respiratory tissues by natural means without any adverse side-effects. The data generated could also be utilized for commercial purposes.

Further, Rosmarinic acid can be potentially used by laboratory workers and painters as nutraceutical to ameliorate the systemic and pulmonary intoxication caused due to occupational related exposure to formaldehyde.

Declarations: The work described has not been published or submitted previously to publication in any for the article is not under consideration for publication elsewhere. if accepted, the article will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

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