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# EFFECT OF 6-GINGEROL ON THIOUREA INDUCED TOXICITY OF LUNGS IN ALBINO RATS

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## ABSTRACT

Pesticides are known for their persistence in the environment along with products of their biotransformation, remaining in and interacting with the environment and living organisms in multiple ways, depending upon their nature and chemical structure, dose and target. The protective effect of 6-gingerol on thiourea induced lung damage in rats has been elucidated in the present study, wherein Wister strain male rats of 200-250gm were selected and divided into 4 groups of 4 animals each. One group given normal saline and treated as control, second group given 0.1 mg/100gm body weight(BW) thiourea, while third was given 0.5 mg/100gm BW 6- gingerol alone and fourth group was given both thiourea and 6-gingerol at mentioned dosage. Experimental setup maintained for 180 days and then sacrificed. Lung tissue dissected and fixed for histological studies. Reduction in body weight as well as lung weight observed, while supplementation with 6-gingerol was observed to bring about improvement in lung and body weight. Granulation, thickening of alveolar walls with inflammation and oedema observed on thiourea induction, while 6-gingerol alone brought about slight inflammation and thickening of alveolar walls. Supplementation of 6-gingerol to thiourea induced group was observed to reduce oedema, lessing of inflammation, thus proving its beneficial effect in alleviating thiourea induced toxicity of the lung.

**Keywords:** 6-Gingerol, Thiourea, Lungs, pesticide toxicity

## 1. INTRODUCTION

In a study of 270 adverse pulmonary reactions leading to hospitalization from two populations, 3.0% were respiratory in nature [1]. Of the reactions considered to be life threatening, 12.3% were respiratory [2]. In a follow-up study, 6 of 24 drug-induced deaths were respiratory in nature [3]. The fraction of inspired oxygen and duration of exposure are both important determinants of the severity of lung damage [4]. Inspired oxygen concentrations between 50% and 100% carry a substantial risk of lung damage, and the duration required is inversely proportional to the fraction of inspired oxygen [5-6]. The biochemical mechanism of the tissue damage during hyperoxia is the increased production of highly reactive, partially reduced oxygen metabolites [7]. There is experimental evidence that a number of drugs and chemicals produce lung toxicity through increasing production of oxidants (e.g., bleomycin, cyclophosphamide, nitrofurantoin, and paraquat) and/or by inhibiting the antioxidant system (e.g., carmustine, cyclophosphamide, and nitrofurantoin) [8-9].

Thiourea is a colourless, lustrous, sand-like, material with a bitter taste. It is used in photography, pharmaceutical and pesticide manufacture, and textile chemicals. This chemical is on the Special Health Hazard Substance List because it is a carcinogen and mutagen. Thiourea can affect when breathed in. Exposure may damage the bone marrow causing reduced red blood cells, white blood cells and/ or blood platelets. Thoiurea may cause skin allergy. If allergy develops, very low future exposure can cause itching and a skin rash. No occupational exposure limits have been established for Thiourea. Thiourea is the class of the organic compounds having sulphur with the general formula $(R_1R_2N)(R_3R_4N)C=S$. Thiourea has versatile applications in field of agriculture. These are used to control the growth of insects, effecting plant growth and seed germination, as fungicide and herbicide.

Herbs and natural products are precious sources of medicinal compounds and their benefits and importance in healing have been well recognized since ancient times. The characteristics and health effects of natural bioactive compounds, especially from plant sources including

spices, have been extensively investigated. Phytochemicals are important compounds found in medicinal plants that are not essential for the normal functioning of the human body, but are active and exert positive effects on health or in amelioration of diseases. Many phytochemicals have been identified though a great many are yet to be identified [10]. According to a report by the World Health Organization, 80% of the population in developing countries depends on traditional medicine for their primary health care, and 85% of traditional medicine is derived from plant extracts [11-14]. Ginger, the rhizome of *Zingiber officinale*, has a long history of use as a traditional medicine in many countries. Ginger (*Zingiber officinale* Roscoe) is one of the most widely used spices in the world. In ancient times, ginger was highly valued for its medicinal properties and it played an important role in primary health care in ancient India and China. Its extracts have been used for managing a variety of ailments, including inflammation, infection, constipation, indigestion, and hypertension [15-16]. Ginger contains a variety of pungent and biologically active compounds, primarily 6-gingerol, 6-shogaol, zingerone, phenolics, and flavonoids. Between identified components, 6- gingerol was reported as the most abundant bioactive compound in ginger with various pharmacological effects including antioxidant, analgesic, anti-inflammatory and antipyretic properties [17-18].The result of recent studies showed that 6-shogaol with lowest concentration in ginger represent more biologically active compounds compared to 6-gingerol[19-20]. Extraction prior to component analysis is the main step for the recovery and isolation of bioactive phytochemicals from plant materials. Analysis and extraction of plant matrices are important processes for the development, modernization, and quality control of herbal formulations. In the present study, 6-gingerol has been used to determine its protective effect on thiourea induced lung damage.

## 2. MATERIALS AND METHODS

### 2.1. Animals

Rats have a short reproductive cycle, short gestation period and produce similar effects, if not all, to that of human beings in a reasonable period of time. So, the selection of albino rats serves a good animal model for the present investigation.

Adult male rats of Wister strain weighing about 150g to 250g were procured from PSG Institute of Medical sciences & Research, Coimbatore, Tamil Nadu, India and acclimatized to our animal house condition for 2 weeks. The animals were housed in well ventilated animal house with constant 12±1h light and dark schedule. They were provided with standard diet and clean water provided *ad libitum*.

### 2.2. Thiourea

Thiourea was purchased from Sigma Aldrich Chemical Company. Thiourea was dissolved in distilled water and injected twice a week as intra peritoneal injection at dose of 0.1mg/ 100g BW for 180 days for study of carcinogenesis.

### 2.3. 6-Gingerol

6-Gingerol was purchased from Sigma Aldrich Chemical Company. 6-Gingerol was dissolved in Dimethyl sulphoxide (DMSO) and injected twice a week as intra peritoneal injection at dose of 0.5mg/ 100g BW for 180 days.

### 2.4. Experimental Design

Experimental setup were complied with the rulings of the committee for the purpose of Control and Supervision of Experimentation on Animals (CPCSEA), New Delhi, India (Registration No: 158/PO/ReBi/SL/99/CPCSEA) and the study were permitted by the Institutional Animal Ethics Committee of the PSG Institute of Medical Science &Research, Coimbatore, Tamil Nadu, India (proposal number: 284/2015/IAEC, Approval: 08.05.2015).The animals were divided into 4 groups as follows:

Group I: Control – given saline
Group II: Thiourea – given thiourea
Group III: 6-Gingerol – given 6-gingerol
Group IV: Thiourea+ 6-Gingerol – given both 0.1mg of thiourea and 0.5mg of 6-gingerol / 100gm/BW

### 2.5. Animal sacrifice

The animals were dissected out and lungs were removed. The organs were cleaned off adhering connective tissues and blood stains, washed in cold physiological saline, blotted on a filter paper and weighed using electronic balance, wrapped in aluminum foil and stored at -20°C in air tight glass containers until assayed for biochemical parameters. Small pieces of lung tissue were fixed in 10% formalin for histological sections and the histological method was followed. The slides were observed under Leica microscope and microphotography obtained.

## 3. RESULTS

### 3.1. Effect on Body Weight

An increase in bodyweight can be seen in the control group only, while all the treatment groups expressed a reduction in bodyweight, the reduction being significant in thiourea treated group. Supplementation with 6-gingerol can be seen to effectively increase the bodyweight (Table 1& Fig. 2).

### 3.2. Effect on Lung Weight

A reduction in lung weight can be seen on treatment with thiourea, when compared to control group. Treatment with 6-gingerol as well as supplementation of 6-gingerol to thiourea induction can be seen to bring about a significant increase in lung weight when compared to thiourea treated group (Table 2& Fig 3).

### 3.3. Effect on Lung Histology (Fig 1)

**Group I (Control)**

Control lungs shows normal alveoli with blood vessels showing slight congestion. There is presence of mild infiltration of chronic inflammatory infiltrates composed mainly of lymphocyte and plasma cells.

**Group II (Thiourea Alone)**

Thiourea treated lung showing granulation, thickening of alveolar walls inflammation and oedema.

**Group III (6-Gingerol)**

Lung treated with 6-gingerol alone showed normal appearing lung, with slight signs of inflammation and thickening of alveolar walls.

**Group IV (Thiourea+ 6-Gingerol)**

Supplementation of 6-gingerol to thiourea treated lungs reduced the oedema formed, with lessening of inflammation. Accumulation of alveolar infiltration also observed.

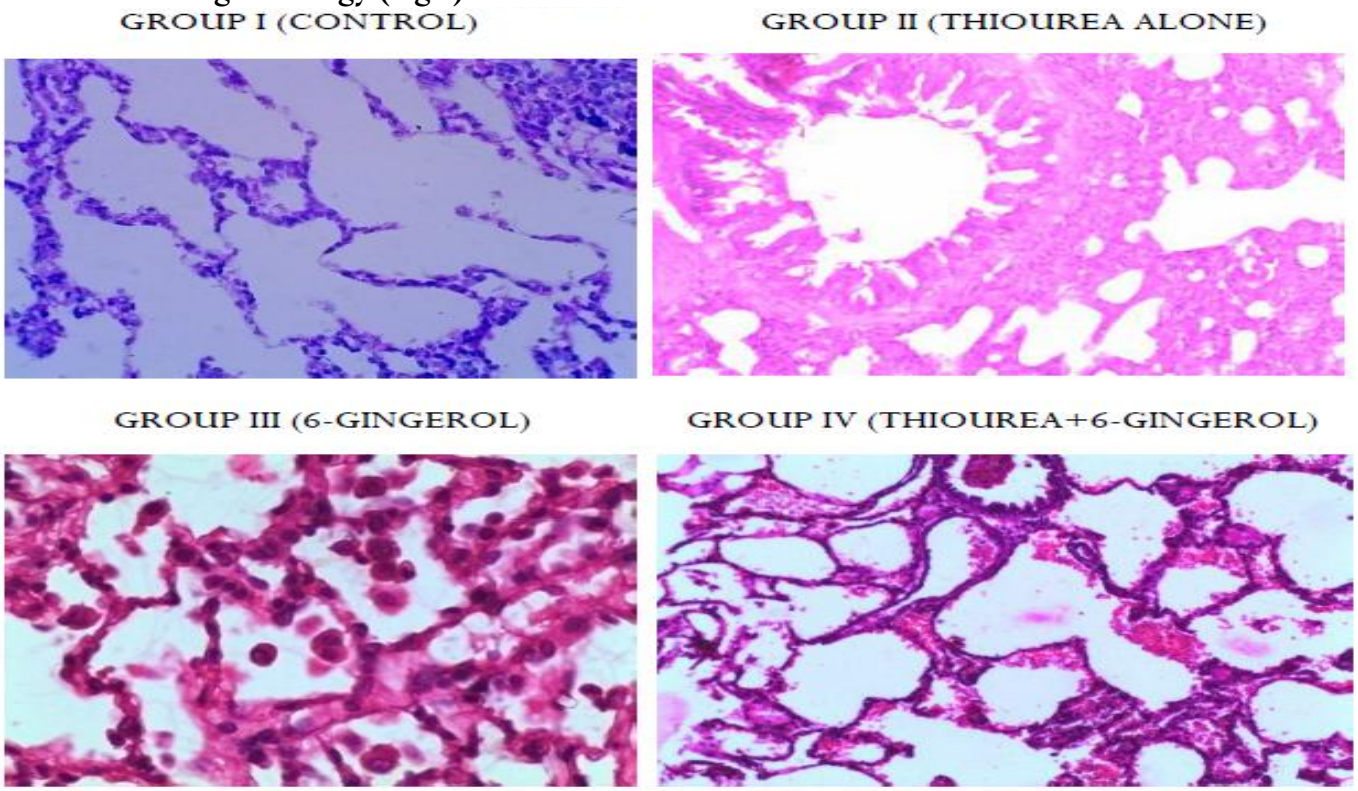


**Fig. 1: Effect of 6-Gingerol on Thiourea Induced Histological Changes in Lung**

**Table.1 Effect of 6-Gingerol on Thiourea Induced Body Weight in Albino Rats**

| Groups | Body Weight (gms) | | % Change |
|---|---|---|---|
| | Initial | Final | |
| I | 248±4.636 | 321±3.316 | 29.4 |
| II | 323±19.733* | 249.4±19.397 | -22.8 |
| III | 318.4±19.206 | 301±18.724 | -5.5 |
| IV | 304.6±17.256** | 297.2±15.866 | -2.4 |

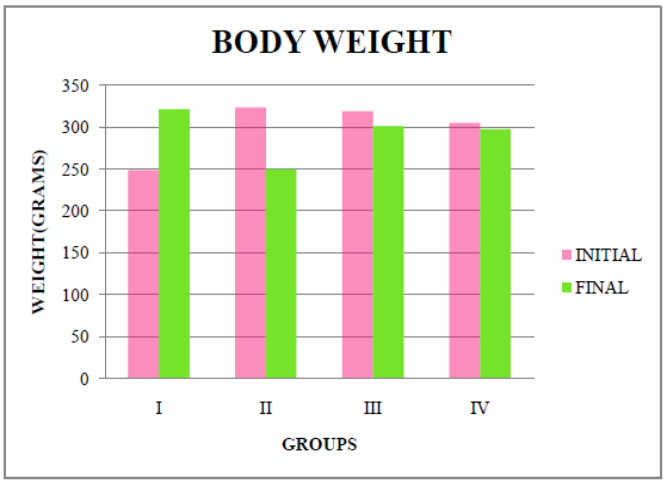


**Fig. 2: Effect of 6-Gingerol on Thiourea Induced Body Weight in Albino Rats**

*Values are expressed as Mean ± S.E.M of five rats.*

**Significance at 5% level of Group I Vs All groups, [a]Significance at 5% level of Group II Vs Group IV*

*I– Control, II- Thiourea, III- 6-Gingerol, IV- Thioura+6-Gingerol*

**Table 2: Effect of 6-Gingerol on Thiourea induced changes in lung weight in albino rats**

| Groups | Lungs Weight(gms) |
|---|---|
| I | 2412±0.078 |
| II | 1.392±0.149* |
| III | 1.854±0.166 |
| IV | 1.814±0.151 |

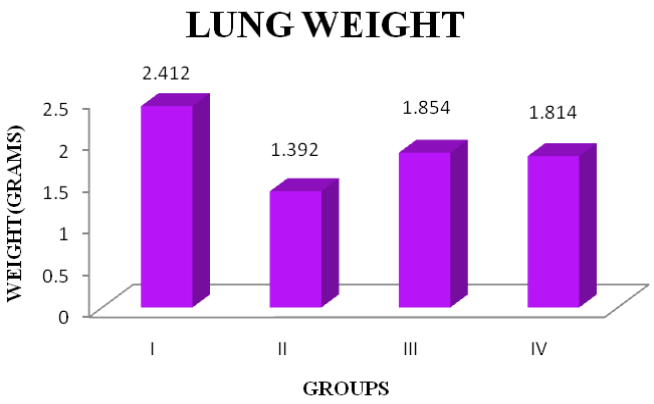


**Fig. 3: Effect of 6-Gingerol on Thiourea induced changes in lung weight in albino rats**

*Values are expressed as Mean ± S.E.M of five rats.*

**Significance at 5% level of Group I Vs All groups, [a]Significance at 5% level of Group II Vs Group IV*

*I– Control, II- Thiourea, III- 6-Gingerol, IV- Thioura+6-Gingerol,*

## 4. DISCUSSION

The lungs are the sites where chemicals are metabolized, as they are the prime organs which are directly exposed to potentially toxic metabolites that are either formed *insitu* or which are present in circulation [21]. Due to bio activation of chemicals in the body and its detoxification, pulmonary damage will be certainly affected. This depends on factors such as preferential exposure or accumulation of parent compounds and metabolites, the specific mechanism of activation of the toxicant and differences in cellular defence mechanisms. Studies have suggested that thiourea derivatives such as α-napthyl thiourea require *insitu* metabolic activation to produce their lung damaging effects [22].

In the present study, thiourea is the xenobiotic under consideration and it is said to damage the vascular endothelium and need to be activated by metabolism in the lung [23]. The pulmonary vascular endothelium will be the primary site for toxic lung damage from preformed reactive products reaching the lung through blood circulation and are activated through cytochrome p-450 independent system in the lung.

Administration of thiourea is seen to bring about a reduction in the bodyweight in all the treatment groups with significant reduction in thiourea treated group. Supplementation with 6-gingerol is seen to effectively increase the bodyweight. The effect of exposure to sodium arsenate and ethanol in male Wister rats increase the body weight. While Diethyl nitrosamine (DEN) treatment did not cause any increase in body weight, supplementation with cinnamon brought about a slight increase, and significant increase on withdrawal of DEN had been reported by Dhanabal [24]. Ginger shows promising anti cancer properties and one of its constituents; 6-gingerol suppresses carcinogenesis in the skin [25], gastro intestinal tract, colon and breast. Its chemopreventive mechanism involves the up regulation of carcinogen, detoxifying, enzymes, antioxidants and showing anti inflammatory activity [26].

Organ weight is an index of swelling, atrophy or hypertrophy [27]. An increase in lung weight, on treatment with aqueous extract of fresh and ripe barriers of *Solanum aculeastrum* in albino rats is reported by Aboyade *et al.*,[28]. Exposure to gasoline vapours caused an increase in lung weight [29]. A slight increase in lung weight on low dose DEN treatment and withdrawal has observed by Dhanabal [24]. This may be due to hypertrophy of the organs due to massive expansion of bronchial tissue with extension of lymphocytes and plasma cells as well as due to the presence of appreciable amount of amorphous material, necrotic cell debris and neoplastic cells in bronchioles and alveolar regions . In

the present study, thiourea induction brought about a reduction in lung weight and treatment with 6-gingerol as well as supplementation of 6-gingerol to thiourea induced rats is seen to bring about a significant increase in lung weight.

The occurrence of massive pulmonary edema and pleural effusion in rats due to thiourea has been documented by Richter [30] and Dieke [31]. This pleural effusion may exert intra thoracic pressure on the lung often causing alveolar edema as well as death, which may be due to sensitivity of mesothelial cell lining layer, as well as, a normal defense response to the presence of excess fluid in the pleural cavity. Hollinger *et al.,* [32] have reported that thiourea can deplete tissue glutathione by as much as 90% after 1 hr. But in the study by Scott *et al.*, [33], there was no evidence to suggest that thiourea depleted lung glutathione levels *in-vivo*.

Many edemagenic agents are said to cause pulmonary endothelial damage allowing invasion of interstitium by excessive fluid, which subsequently escape through clearance by lymphatics or passing into alveolar air ways or passage into pleural cavity. Butylated hydroxytoluene (BHT) causes damage to Type I pneumocytes in mice but apparently not in rats. There is evidence that BHT may undergo metabolism related covalent binding to lung tissue and that this may be related to its pulmonary toxicity *in-vivo* [34].The pulmonary vascular endothelium will be the primary site for toxic lung damage from preformed reactive products which reach the lungs from blood stream. Thiourea damage the vascular endothelium when they are activated through cytochrome $P_{45}$ independent system in the lung. The main constituents of 6-gingerol are quickly absorbed and detected in serum as glucuronide and sulphate conjugate with the majority being detected as glucuronide metabolites[35].

Lung tissue and the alveolar lining fluid contain high levels of antioxidants that presumably protect against oxidant and free radicals. Cytotoxic drugs trigger the formation of RO metabolites with phagocytic cells like monocytes, macrophages and neutrophils and result in direct injury to lungs. They also initiate a metabolic cascade that produces immunoreactive substances like prostaglandins and other cytokines which in turn lead to inflammation and lung damage to counter balance the amplified effects of immunological system, that may result in tissue damage and hypersensitivity, leading to pulmonary injury and finally to pulmonary fibrosis . Normally proliferation of fibro blasts lead to collagen deposition which is helpful in repairing of lining tissue injury. But excessive deposition of collagen can result in organ structure impairment.

Exposure to the vapours of two kinds of motor gasoline (Vehicle fuel in Egypt), one leaded(G1) and the other unleaded(G2),on rat lungs for 30 minutes daily along six consecutive weeks caused intensive histological alterations in the lining epithelial cells of the bronchioles. These changes included detachment and necrosis of the epithelial cells. Some bronchioles were even clogged with neoplastic cells [29]. The histopathological changes manifested as accumulation of inflammatory cells, fibrosis and congestion of vessels and blood capillaries.

The histological outline of the lungs of the animals in the DEN treatment group revealed significant cyto architectural alteration and/or disruption as well as enlargement of the alveoli and the alveolar sacs. The massive enlargement of the alveoli and bronchiolar occlusion could have been a result of direct toxicity or could have resulted from transportation of toxic substances from other organs like the liver and kidney to the lungs. Supplementation with cinnamon and withdrawal of DEN treatment seems to have some recuperative effect on lung histology [36].

Pertaining to lung histology in the present study, thiourea administration was observed to bring about granulation, thinning of alveolar epithelium with apparent inflammation and oedema while treatment with 6-gingerol caused slight thickening of alveolar wall with signs of inflammation. Supplementation of the same to thiourea induced groups caused a reduction in oedema and lessening of inflammation, along with accumulation of alveolar infiltration.

The lungs revealed varying degrees of pulmonary congestion and edema, while those in groups IV exhibited pulmonary edema, varying degrees of pulmonary congestion, and haemorrhages. The lesions were generally observed in most of the toxicity studies with cypermethrin. Patel *et al.,* [37] reported mild-to-moderate congestion, edema, hemorrhage, and focal areas of emphysema in cypermethrin- intoxicated calves. Manna *et al.*, [38] reported the same lesions in rats intoxicated with single and repeated doses of cypermethrin. Congestion, hemorrhage, and thickening of the interalveolar septa were observed in rats intoxicated with cypermethrin.

Therefore, pulmonary injury may be a prominent effect of certain classes of chemicals that undergo bioactivation in the body. The specific types of lung cells damaged may depend upon factors such as preferential exposure or

accumulation of parent compounds and /or metabolites, differences in cellular defense mechanisms, or the specific mechanism of activation of the toxicant. Prior knowledge about the metabolism, disposition and mechanism of bioactivation of a particular compound may allow prediction of the type of lung cell damage it is likely to produce [21].

## 5. CONCLUSION

From the presents study, it can be inferred that lungs when exposed to potentially toxic substances like thiourea, lead to production of metabolites which are either formed *in situ* or which are present in the circulation. Further studies with different more effective dosage and duration may facilitate the elucidation of thiourea's toxic effect.

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