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Research Article

Amelioration of lead nitrate induced pulmonary toxicity by Garlic essential oil in inflammatory markers of Swiss albino male mice

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Abstract
Lead is a toxic heavy metal that causes harmful effects on human health. Its prolonged use interferes with the pulmonary tissue, resulting in alterations in the normal level of transcription factors and cytokines. So, to restore these parameters altered by lead nitrate (LN) $Pb(NO_3)_2$, the present study aimed to test natural therapeutic agents like *Allium sativum* (AS) and its defensive role in mitigating lead (Pb) induced toxicity in Swiss albino male mice model. For this one-month study, 36 mice were divided into 6 Groups. The Groups were categorised as Group I (control/untreated), Group II a (lead nitrate (LN))(50mg/kg), Group II b (LN+ low dose of garlic essential oil (GEO) (50mg/kg)), Group II c (LN+ high dose of GEO) (80mg/kg), Group II d (LN with standard drug (silymarin) (25mg/kg)), Group II e (LN + vehicle olive oil). The experimental results revealed an elevated level of NF-kB($P< 0.001$), TNF-α and IL-6 ($P < 0.05$ for both) and a decreased level of IFN-ϒ ($P<0.05$) and IL-10 ($P < 0.01$) in Lead-intoxicated pulmonary tissues of mice. Conversely, GEO exhibited promising anti-inflammatory properties by attenuating the alterations caused by LN. The present study demonstrated the significant effectiveness of a high dose of garlic bulb essential oil in reducing inflammation in the pulmonary tissues of an animal model exposed to lead nitrate. Notably, the low dose also exhibited efficacy for certain inflammatory markers. Further optimization of Garlic Essential Bulb Oil (GEBO) doses is warranted to enhance its therapeutic potential. This study expands the scope of exploring natural interventions for mitigating lead-induced toxicity.

Keywords: Garlic essential oil, Heavy metal toxicity, Inflammatory markers, Pulmonary tissues, Therapeutic properties

INTRODUCTION

Heavy metals are naturally found as non-biodegradable elements with high atomic number and density. These heavy metals are categorized into essential and non-essential metals where essential metals such as cobalt, manganese, copper, iron, molybdenum, zinc and selenium are important for enzyme functions, while non-essential metals such as lead, mercury, vanadium, cadmium, tungsten and plutonium are considered toxic and can lead to health issues including cancer, allergies, and autoimmunity (Anka *et al.* 2022).

Lead (Pb) is a common occupational and environmental hazard worldwide. Due to the toxic pervasiveness of lead in the environment, it remains a matter of public concern. There are several ways through which Pb enters the human body. Inhalation is one of the routes through which Pb enters the body from various sources, including residential paints, smoking, burning of gasoline, tobacco and many more. Toxicity of Lead depends on the exposure level. High-level toxicity of Pb causes severe effects on children, such as a decline in attention span, elevation in dullness and irritability, and shorter attention span in CNS (Central nervous system), which results in headache, coma and even death. It contributes 0.6% of the global disease burden (Zhang *et al.*, 2024).

Among the various organs, the lungs are the primary site for Pb exposure and accretion, comprising diverse cells (Attafi *et al.*, 2022). Pb weakens the humoral immune response which results in decreased antibody production. Investigations have demonstrated that Pb manifestation alters the function of several immunocytes and the construction of inflammatory mediators

and cytokines like IL-6, IL-10, TNF-α, IFN-ϒ in both human and animal studies. Transcription factor, NF-κB, helps to regulate these cytokines and immunomodulatory markers, which play an important role in organ inflammation and apoptosis (Attafi *et al.*, 2022). However, metal chelators, for instance, meso,-2,3-dimercaptosuccinic acid (DMSA) and mono isoamyl DMSA (MiADMSA), are approved treatments for lead intoxication; they form an insoluble complex with lead and thereby reduce its toxicity. However, these chelators cannot extract Pb from the body tissues because they cannot cross the cell membrane to entangle intracellular Pb, as they are hydrophilic or lipophobic. To capture intracellular Pb, drugs with lipophilic properties are needed (Sharma *et al.*, 2010) (Mehrandish *et al.*, 2019). From ancient times, natural herbs have been used for their medicinal properties and ability to treat various ailments. Garlic (*Allium sativum*) is one such herb that belongs to the family Liliaceae, possessing lipophilic properties. It is commonly used in medicinal products and is known for its broad range of pharmacological properties, such as immunomodulatory, hepatoprotective, anti-mutagenic, hypo-lipidemic, antibacterial, antithrombotic, and anticancer effects. Previous research highlights that garlic can be used in various forms, such as tablets, raw, boiled, cooked or dried. Economically disadvantaged individuals and societies can easily incorporate garlic into food due to its cost-effectiveness and easy availability in the market (Alodeani *et al.*, 2014). Diallyl tetra sulphides (DADS) and diallyl trisulphides are key sulphur components present in garlic essential oil (GEO). Previous research reported the anticancer activity of DADS against several tumour cells (Mitra *et al.,* 2022). Therefore, keeping the positive aspect of *Allium* in mind, this research study was planned to analyse the therapeutic effect of GEO on lead nitrate (LN)-altered transcription factor, inflammatory mediators and cytokine levels in Swiss albino male mice lungs.

MATERIALS AND METHODS

Chemical reagents

The Central Drug House (India) was the source of lead nitrate Pb $(NO_3)_2$. Other reagents were sourced from Sisco Research Laboratories, India, SD Fine Chemicals, India, HIMEDIA, India, Qualigens (India/ Germany) and Central Drug House (India). All the chemicals of analytical grade were used.

Plant material

Allium sativum (Garlic) aggregated from the botanical garden of Banasthali Vidyapith, India, was used in the experimental study. It was identified as a local variety from Krishi Vigyan Kendra (BV) and submitted to the herbarium with the authentication number BURI-1710/2022 in the Bioscience and Biotechnology Department, BanasthaliVidyapith, Rajasthan, India.

Oil extraction and the route of administration

Garlic essential oil was extracted via the Hydro-distillation method. Garlic was peeled and mixed with distilled water to create a slurry using homogenizer mixture. The slurry underwent hydro-distillation process at 90°C for 4 hours and the oil was collected and stored at 4 °C for experimental purposes (O'Gara *et al.,* 2000).

Experimental animal

Swiss albino male mice (*Mus musculus*) 2-3 months old were used for the experimental study. They were procured from Lala Lajpat Rai University, (Hisar) Haryana, India & housed in propylene cages with access to water and food (Chow food, Aashirvad Industries Chandigarh, India) throughout the study. The mice were acclimatized approximately 1 week before the start of the experimental study. Air-conditioned room with a temperature and humidity of 25°C ± 3°C and 50% ± 5% was used to conserve these animals. Further, a 12-hour day -night cycle was also maintained.

Ethical approval

Ethical approval for the experimental study was obtained from the Institutional Ethical Committee of Banasthali Vidyapith (approval no. BV/IAEC/ January/2020/10).

Experimental prototype

The study was conducted over 30 days, during which double distilled water and chow food were provided continuously from Aashirvad Industries, Chandigarh, India. Lead nitrate, garlic essential oil (GEO), silymarin (standard drug), and olive oil (vehicle) were administered orally via oral gavage. A total of thirty-six (36) mice were split into 6 Groups, which were named group I (Control), group IIa (Lead nitrate treated), group IIb (LN+ GEO low dose), group IIc (LN+ GEO High dose), group IId (LN+ Silymarin), group IIe (LN+ Olive oil), with 6 mice in each group. The administration of the toxicant began on the first day (LN was suspended in distilled water and used as a toxicant at a concentration of 50mg/kg, given to all Groups for 30 days except control Group animals) (Sharma *et al.,* 2010), while medicinal drug (Garlic essential oil doses) were prepared in vehicle oil: Low dose of GEO was 50mg/kg and High dose was 80mg/kg) (Zeng *et al.,* 2008), standard drug silymarin (25mg/kg)(Singh *et al.,* 2018 *)*, and vehicle were given from the 12th day of study along with the toxicant. On the last day of the study, the mice were given rest overnight, and before dissection, their weight was measured by a weighing machine. After sacrifice, lung tissues were immediately collected, washed with ice-cold saline, and stored in phosphate buffer saline

(PBS) at -20°C for further use. These doses of toxicant, GEO and standard drug were selected based on previous research, including Sharma *et al.,* (2010); Zeng *et al.* (2008); and Singh *et al.* (2018 *)* (Table 1).

Tissue homogenate preparation

After the dissection, the lung tissues were procured, weighed, and placed into a petri plate for mincing. The minced tissue and the homogenate buffer (pH-7.4, 0.1M) were then transferred to a centrifugation tube, and the homogenization process was carried out using a tissue homogenizer (Yorcohigh-speed tissue homogeniser). Subsequently, centrifugation was performed at 10,000 rpm for 10 minutes at 4°C, followed by discarding the pellet and storing the supernatant at -20° C for further use.

Inflammatory markers

In this experimental study, inflammatory markers and cytokine levels were analysed in pulmonary tissues of mice subjected to LN. Cell-mediated responses and inflammatory-related genes were controlled by the main factor NF-kB.

The inflammatory status of pulmonary tissues in mice was determined by enzyme-linked immunosorbent assay (ELISA) kits: NF-kB p65, TNF-α, and IFN-ϒ, which were purchased from Invitrogen and Thermo Fisher Scientific company with Catalog No: 85-86,081-11; BMS223-4; BMS228, respectively. Proquantum immunoassay kits from Invitrogen, Thermo-Fisher Scientific (Catalog No: A35573, A35590) were used to analyse the concentration levels of IL-6 and IL-8 in the pulmonary tissues of mice.

Statistical analysis

This experimental study analysed the data using the software SPSS 20.The statistical data was manifested as mean ± SEM, and P< 0.05, P<0.01 and P<0.001 were set for the significant level between Groups. Tukey's test (*post hoc* pairwise analysis) and One-way ANOVA were employed to compare the experimental Groups.

RESULTS

The present study indicated that the inflammatory level of NF-kB was significantly increased in Group IIa animal (P< 0.001), while it decreased significantly in Group IIb and IIc mice after the administration of both the doses (low and high) of GEO with the significant values of P<0.01 and P< 0.001, respectively. Further, NF-kB levels significantly decreased in Group IId animals (P<0.001), while a non-significant decrease of NF -kB was observed in Group IIe animals (Fig. 1 A).

Additionally, NF-kB-activated pro-inflammatory factors (TNF-α and IL-6 levels) was upregulated with a significance value of P < 0.05 for both, whileIL-10 and IFN-ϒ levels were downregulated with a significance value of P < 0.05 and P < 0.01 respectively in Pb-intoxicated Group IIa mice in comparison to normal subjects.

The concentration of TNF- α in Group IIb and IIc mice was decreased when compared to Group IIa mice with significant values of P< 0.05 and P< 0.001. However, a high dose was more efficient than a low dose in restoration of TNF-alpha. In contrast, a significantly low TNF -α was seen in Group IId mice (P< 0.01), while a non-significant TNF- α was observed in Group IIe animals.

Apart from these, pro-inflammatory factor IL-6, the interleukin level declined in both low and high-dose animal Groups (II b and II c) compared to treated Group animals (P<0.01 and P<0.001 respectively). So, it can be inferred that the high dose more efficiently recovered the interleukin-6 level than the low dose. Significant IL-6 P<0.01 and P<0.05 regression was observed in Group II d and Group II e animals compared to the Group II a mice. Fig.1D shows that IL-10 interleukin level was significantly elevated in Group II b and II c mice (P<0.05 and P<0.001, respectively). However, a non-significant decrease of IL-10 was observed in Group II d and Group II e mice compared to lead nitrate-treated Group mice.

Further, an insignificant rise of IFN-gamma was observed in low-dose Group IIb mice, while a significant elevation was observed in high-dose treated Group II c (P<0.05) compared to Group I animals. Further, non-significant elevation of IFN-gamma was observed in silymarin and olive oil-treated Groups IId and IIe mice.

DISCUSSION

Humans are affected by the heavy metals present in their environment, which is harming them by using day to day daily necessities. In response to this concern, the present study explored the potential of natural plant formulations (GEO) to address this problem. The study investigated garlic essential oil as a potent remedy to restore the balance between toxic elements and overall well-being. Among all, lead nitrate is one of the heavy metals that causes detrimental effects to man. The skin and organs easily absorb this. On absorption, these xenobiotics first target the lungs (Sarkar *et al.,* 2024).

The present study on the inflammatory marker parameters like NF-kB, TNF- α, IFN- ϒ, IL-6 and IL-10 indicated that lead toxicity elevated the level of NF-kB, interleukin-6 & TNF- α and decreased the level of IL-10 and IFN-ϒ in animals of Group II a in comparison to the Group I animals which were control mice. Here, the manifestation of cytokines (IL-6 and TNF-α) was promoted by the potent inflammatory mediator NF-kB (Imam *et al.,* 2015; Liu *et al.,* 2017), which has become apparent in the current results. Previous research also reported that Pb can stimulate NF-kB (Korashy *et al.*,

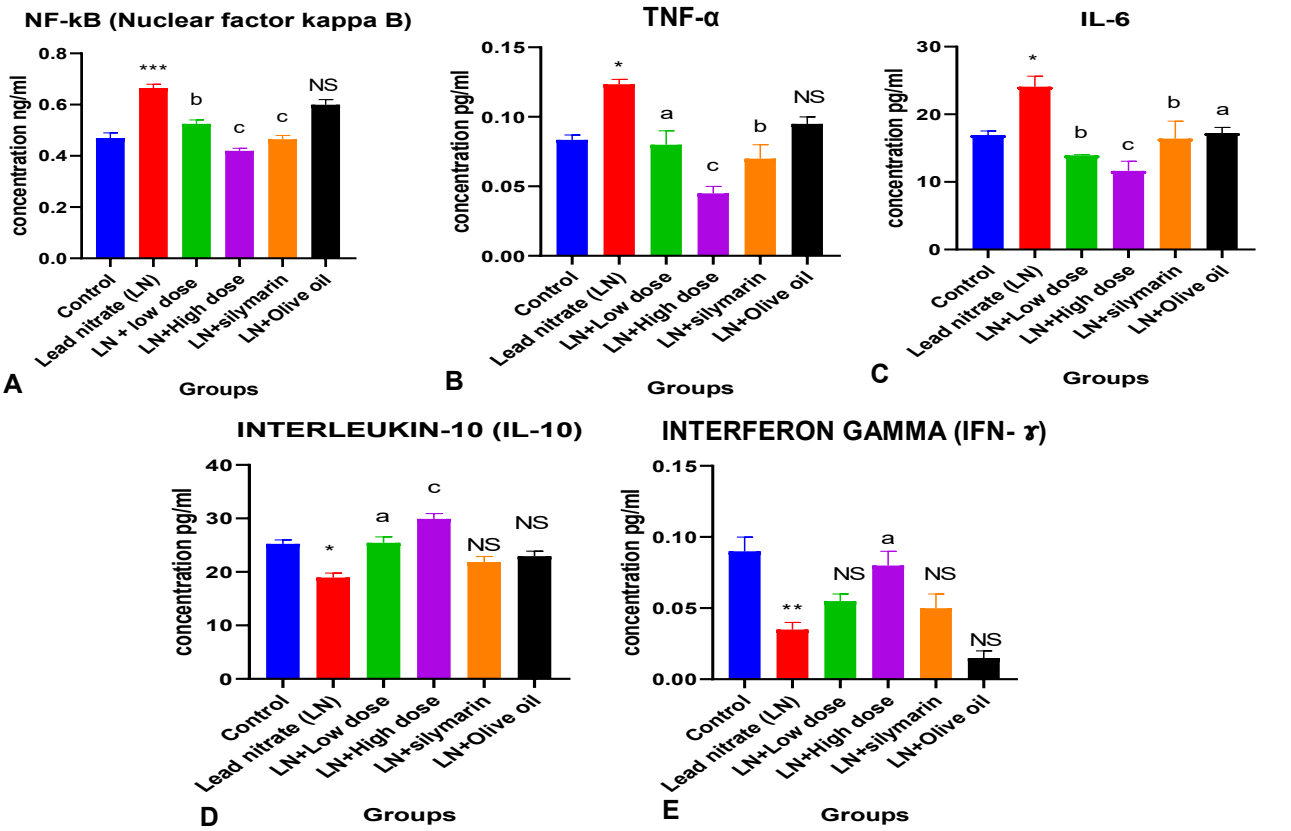

Fig.1. *Showing the level of lead nitrate and garlic essential oil in different Groups of the experimental study; A: NF-kB (Nuclear factor kappa B), B: TNF-α (Tumor necrosis factor α), C: IL-6 (Interleukins-6), D: IL- 10 (Interleukin -10), E: IFN -ɤ (Interferon-ɤ). NS stands for non-significant; Significant difference in the data manifested as - P<0.05 , *P<0.01 , ** P<0.001 ***lead nitrate compared to the control Group. P<0.05[a], P<0.01[b], P<0.001[c]. Other treated Groups compared with LN treated Group*

2008).Once NF-kB is released, IKK phosphorylation will be triggered. Then it leads to IkB-α ubiquitination and proteosomal destruction. As a result, NF-kB becomes activated, which then translocates in the nucleus and controls the transcription of target genes(Yang *et al*., 2016). However, in this study, results demonstrate that GEO high dose significantly reduced the Lead nitrate-induced NF-kB translocation into the nucleus via reducing IkB-α degradation, in which IKK intervenes. Therefore, the preventive exposure of GEO in Lead nitrate-induced toxicity is likely via attrition of inflammatory response and limited yield of inflammatory cytokines (Liu *et al.,* 2018). Among many compounds in GEO, Quercetin may be the main component in suppressing activated B cells NF-K light chain enhancer (Yamaguchi *et al.,* 2011). Besides, silymarin and olive oil also contributed to reverting the cause to some extent in Group II d and II e animals. Here, based on observations, silymarin may also possibly try to inhibit the Ik-B phosphorylation and degradation, which results in the inactivation of NF-kB, due to which it remains in the cytoplasm and does not translocate in the nucleus. On the other hand, oleuropein and hydroxytyrosol are the polyphenols present in olive oil that may be tried to inhibit the NF-kB activation to some extent by suppressing upstream signalling pathways, oxidative stress, and inflammation in Group II e animals of the experimental study (Fig. 2)

In this study, IL-6 and TNF- α were also examined, and LN acted as the main stimulus that triggered the inflammatory reaction due to its significant amount of harmful components. Particularly when the respiratory tract gets exposed to Pb, inflammatory cells keep infiltrating the lesions exposed to LN (Yücesoy *et al.*, 1997; Yamaguchi *et al.,* 2011). However, the present study aligns with Zhang *et al*. (2020), who state that neutrophils are among the inflammatory cells that have invaded the body and play a significant role in causing pathological changes in the respiratory tract. Previous researches conclude that neutrophils activated by LN exposure release several stimulating factors like cytokines, chemokines, growth factors, chemo-attractant, Reactive oxygen species and proteases. These factors eventually lead to an elevation in neutrophil infiltration and exacerbate the destruction of normal pulmonary (alveolar) structure, resulting in elevation of TNF- alpha & IL-6. Garlic has been used since ancient times due to its beneficial pharmacological properties. Previous studies

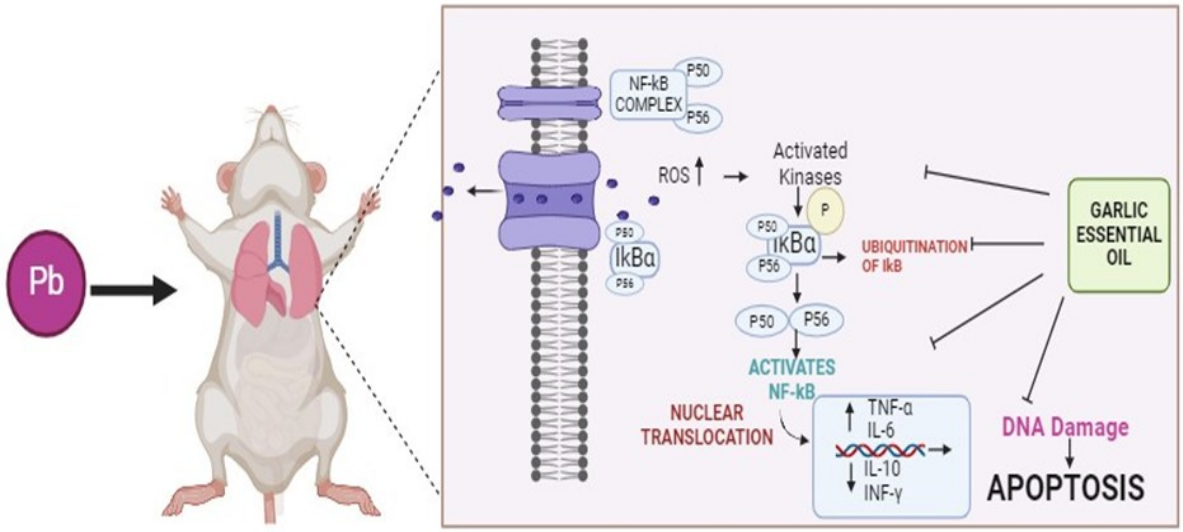

Fig. 2. *Systematic representation showing the proposed mechanism of lead nitrate affecting mice pulmonary tissues and how garlic essential oil attenuates the damage in DNA and inflammatory markers.*

Table 1. Grouping of mice for experimental study on lead nitrate intoxication

Groups	Number of mice	Toxicant	Geo doses	Amount of toxicant and drug administered (mg/kg)	Day of administration	Day of dissection
I Control	6	Control	Distilled water		Day 1 to Day 30	On 31th day
II a	6	Lead Nitrate		50	Day 1 to Day 30	
II b	6	Lead Nitrate	GEO Low Dose	50	LN FOR 30 DAYS GEOLD FROM 12TH DAY	
II c	6	Lead Nitrate	GEO High Dose	80	LN FOR 30 DAYS GEOHD FROM 12TH DAY	
II d	6	Lead Nitrate	Silymarin	25	LN FOR 30 DAYS SILYMARIN FROM 12TH DAY	
II e	6	Lead Nitrate	Olive Oil		LN FOR 30 DAYS OLIVE OIL FROM 12TH DAY	

showed that garlic possesses sulphur moieties, which act as a therapeutic agent in various illnesses against heavy metal toxicity (Cazzola *et al.,* 2012). The results of this study summarise that Quercetin & DADS of GEO potentially reduced the elevation of interleukin-6 and TNF- α in the animals of Group IIc by limiting the activation of cytokines and transcription factors in the pulmonary tissues of mice which aligns with the research done by Ko *et al.,* 2018.

Simultaneously, the study also focuses on the IL-10 and IFN- ɤ. The potent anti-inflammatory cytokine like IL-10 is generated during innate and adaptive immune responses. Here, we noticed that IL-10 and IFN- ɤ in the pulmonary tissues of Pb exposed were significantly decreased (Boskabady *et al.,* 2018). This finding confirms with the previously published research, which showed a connection between oxidative stress, tissue damage and inflammation (Sharma *et al.,* 2024). Further, GEO treatment helped to overcome the toxicity to the minimum level (Dorrigiv *et al*., 2020), but standard drugs and vehicles, to some extent in some of the parameters, protected from metal toxicity.

Conclusion

The present experimental study investigated the potential protective therapeutic properties of orally administered garlic essential oil in mice. The study indicated that high dose of GEO (80mg/kg)may protect the tissues, as evidenced by the analysis of inflammatory markers (NF-kB, IL-6, IL-10, TNF-α and IFN-ɤ). This suggests that garlic essential oil, derived from *A. sativum*, may offer a protective function without any discernible side effects when consumed in the appropriate

dosage and form. Further, extensive study is required to optimize doses of garlic essential oil.

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Conflict of interest

The authors declare that they have no conflict of interest.

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