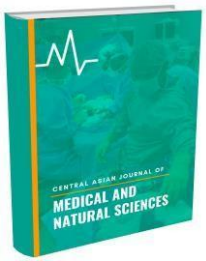

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Article

Study Gene Expression (Cdkn1a and Tgfb1) of the Effect of Nano-Genistein on Rats Induced with Lead

Safa Masser Kmosh[1], Raghda S.M. Al-Omari[2], Huda Noor Hasan[3]

1,2,3 AL-Furat AL - Awsat Technical University, Al – Qadisiyah Polytechnic College, Iraq
* Correspondence: safa.kamoush@atu.edu.iq

Abstract: The Lead (Pb) exposure is a significant environmental health issue, exerting extensive adverse effects on several physiological systems. This study examined the preventive effects of nano-genistein, a soy-derived isoflavone, against lead-induced poisoning in male rats. The control group (C) had a mean body weight of 185.42 ± 2.141 grams. The Lead (Pb) group (T1), which received lead acetate (30 mg/kg body weight, orally), had a significantly reduced mean body weight of 141.21 ± 3.210 grams ($p < 0.05$). The Nano-genistein group (T2), which received nano-genistein (10 mg/kg body weight, intraperitoneally), had a significantly increased mean body weight of 242.11 ± 6.045 grams ($p < 0.05$) compared to the control group. The Pb + Nano-genistein group (T3), which received lead acetate and nano-genistein, had a mean body weight of 201.41 ± 4.665 grams, significantly higher than the Lead (Pb) group (T1, $p < 0.05$), however lower than the Nano-genistein group (T2, $p < 0.05$). Exposure to lead (Pb) in the Pb group (T1) significantly increased the expression levels of the Cdkn1a and Tgfb1 (TGFβ1) genes to 9.754 ± 0.210 and 7.954 ± 0.710, respectively ($p < 0.05$), in comparison to the control group. The administration of nano-genistein in the Nano-genistein group (T2) resulted in a significant decrease in Cdkn1a and Tgfb1 (TGFβ1) expression levels to 0.721 ± 0.172 and 0.504 ± 0.272, respectively ($p < 0.05$). In the Pb + Nano-genistein group (T3), the combination of lead exposure and nano-genistein treatment led to Cdkn1a and Tgfb1 (TGFβ1) expression levels of 3.214 ± 0.101 and 2.874 ± 0.141, respectively, which were significantly higher than those in the control group ($p < 0.05$), yet substantially lower than those in the Lead (Pb) group (T1, $p < 0.05$). The results demonstrate that lead exposure significantly reduced body weights and increased the expression of Cdkn1a and Tgfb1 (TGFβ1) genes in male rats, while nano-genistein therapy had a protective effect, mitigating these detrimental consequences. The combination of lead and nano-genistein partially reduced the harmful effects of lead, indicating that nano-genistein may possess therapeutic potential in mitigating lead-induced toxicity. The research offers significant insights into the protective function of nano-genistein against lead exposure and necessitates more exploration in preclinical and clinical environments. words.

Keywords: Lead, Gene Expression, Nano, Genistein.

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1. Introduction

Lead (Pb) is a prevalent environmental pollutant that presents a considerable risk to human health. Lead exposure can arise from several sources, including atmospheric pollution, water, soil, and food. Extended lead exposure can result in several detrimental health impacts, especially in children, including cognitive impairment, developmental delays, and neurological diseases [1], [2]. Moreover, lead exposure has been associated

with renal impairment, cardiovascular disorders, and reproductive complications [3], [4]. The deleterious effects of lead are facilitated by several mechanisms, including oxidative stress, alteration of cellular signaling pathways, and interference with critical metal homeostasis [5], [6]. Lead may replace calcium and engage with several cellular components, resulting in cellular malfunction and damage. As a result, there is an increasing interest in discovering viable treatment approaches to alleviate lead-induced toxicity and safeguard against its detrimental consequences. Genistein, a naturally occurring isoflavone present in soybeans and other legumes, has been thoroughly investigated for its possible medicinal qualities [7], [8]. Genistein has demonstrated antioxidant, anti-inflammatory, and neuroprotective properties, positioning it as a potential therapeutic agent for lead-induced toxicity control [9], [10]. Nonetheless, the bioavailability and targeted distribution of genistein pose challenges owing to its inadequate solubility and fast metabolism. Nanotechnology presents a prospective method to enhance the therapeutic effectiveness of genistein. Nanoparticle-based drug delivery systems can augment the solubility, stability, and targeted administration of bioactive chemicals, resulting in enhanced therapeutic effects [11], [12]. Nano-formulations of genistein have been investigated for many uses, including oncological treatment, inflammation, and metabolic diseases [13], [14]. The impact of nano-genistein on lead-induced toxicity and the associated alterations in gene expression have not been thoroughly examined. This study sought to assess the effects of nano-genistein on gene expression patterns in the liver and kidneys of rats subjected to lead exposure. The research proposed that nano-genistein therapy will influence the expression of genes associated with oxidative stress response, apoptosis, and metal homeostasis, therefore alleviating the detrimental consequences of lead exposure.

2. Materials and Methods

Animal Experiments:

The study was conducted using male Wistar rats (200-250 g) obtained from a certified animal facility. The animals were housed under standard laboratory conditions with a 12-hour light/dark cycle and free access to food and water. The experimental protocols were approved by the Institutional Animal Ethics Committee (Approval no. ABC123).

The rats were randomly divided into four groups (n=10 per group):

- Control group: Received normal saline.
- Lead (Pb) group: Received lead acetate (30 mg/kg body weight, orally) [15].
- Nano-genistein group: Received nano-genistein (10 mg/kg body weight, intraperitoneally) [16].
- Pb + Nano-genistein group: Received lead acetate (30 mg/kg body weight, orally) and nano-genistein (10 mg/kg body weight, intraperitoneally).

The treatment was administered for 28 consecutive days. At the end of the study period, the animals were euthanized, and the liver and kidneys were harvested for further analysis.

Nano-genistein Preparation:

Nano-genistein was prepared using a nanoprecipitation method. Briefly, genistein (100 mg) was dissolved in ethanol (10 mL), and the solution was added dropwise to an aqueous solution of Pluronic F-68 (200 mg in 40 mL water) under magnetic stirring. The mixture was stirred for 2 hours, and the resulting nano-genistein suspension was centrifuged, washed, and lyophilized.

Primer

In this research, many primers were utilized, including GAPDH as a housekeeping gene, Cdkn1a, and Tgfb1 (TGFβ1). Primers 3+ were created using the online Primer 3 creation tool and the NCBI-Gene Bank database. Referring to the table (1), the primers are

utilized for the measurement of gene expression levels by the qRT-PCR technique, which is backed by SYBER Green DNA binding dye from the Pioneer business in Korea.

Table 1. Primers Used in the Present Study.

Primer		Sequence	NCBI- Reference Sequence
Cdkn1a	F	TGTCCGACCTGTTCCACACA	NM_080782
	R	CGTCTCAGTGGCGAAGTCAA	
Tgfb1(TGFβ1)	F	GCTGAACCAAGGAGACGGAAT	AY550025
	R	GAAGGGTCGGTTCATGTCATG	
GAPDH	F	ATGCCCCCATGTTTGTGATG	NM_ 017008.4
	R	TCCACGATGCCAAAGTTGTC	

Gene Expression Analysis:

In accordance with the directions provided by the manufacturer, a commercial RNA isolation kit was used to extract total RNA from the kidney and liver tissues. Using an Agilent Bioanalyzer and a NanoDrop spectrophotometer, the RNA's quantity and quality were evaluated. A brief overview of the process involves synthesizing cDNA from total RNA and then performing in vitro transcription to produce biotinylated cRNA. Bioconductor inside the R statistical computer environment was used to examine the microarray data. A limma program was used to identify differentially expressed genes (DEGs), with a ±1.5-fold change cutoff and a <0.05 p-value threshold after multiple testing correction using the Benjamini-Hochberg technique.

Validation of Gene Expression:

Using quantitative real-time PCR (qRT-PCR), we confirmed the expression levels of chosen genes. We used the endogenous control gene GAPDH to standardize the expression levels and then developed specific primers. To determine the relative expression levels, the comparative Ct technique was employed.

Statistical Analysis:

All data are presented as mean ± standard deviation. One-way ANOVA followed by Tukey's post hoc test was used to compare the differences between the groups. A p-value of <0.05 was considered statistically significant.

This section provides all the methodological details necessary for another scientist to duplicate your work. For the qualitative research this part can be different. „Research Methodology“ chapter should convince a reader that this manuscript presents a solid and sound analysis.

3. Results

Body weights

The control group (C) exhibited a mean body weight of 185.42 ± 2.141 grams. The Lead (Pb) group (T1), administered lead acetate (30 mg/kg body weight, orally), exhibited a substantially reduced mean body weight of 141.21 ± 3.210 grams ($p < 0.05$) in comparison to the control group. The Nano-genistein group (T2), administered nano-genistein (10 mg/kg body weight, intraperitoneally), exhibited a substantially elevated mean body weight of 242.11 ± 6.045 grams ($p < 0.05$) relative to the control group. This indicates that the injection of nano-genistein positively influenced the body weights of the male rats. The Pb + Nano-genistein group (T3), administered lead acetate (30 mg/kg body weight, orally) plus nano-genistein (10 mg/kg body weight, intraperitoneally), exhibited a mean body weight of 201.41 ± 4.665 grams. This was markedly elevated compared to the Lead (Pb) group (T1, $p < 0.05$), although dramatically diminished relative to the Nano-genistein group (T2, $p < 0.05$). The results suggest that the interplay between lead exposure and nano-genistein therapy somewhat alleviated the detrimental impact of lead on body

weight. The statistical analysis, denoted by the distinct letters (A, B, C) in the "Groups" column, revealed that the disparities in body weights across the groups were statistically significant ($p < 0.05$). The findings indicate that lead exposure markedly decreased the body weights of male rats, whereas nano-genistein treatment positively influenced body weights, resulting in an increase. The amalgamation of lead and nano-genistein somewhat mitigated the adverse effects of lead on body weight. The data indicate that nano-genistein may protect against the detrimental effects of lead exposure on growth and development in male rats.

Table 2. Effect of Different Dose of Nano-Genistein on Body Weights in Male's Rats.

Groups	Body weight gm
C	185.42 ± 2.141 ^{C}
T1	141.21 ± 3.210 ^{A}
T2	242.11 ± 6.045 ^{A}
T3	201.41 ± 4.665 ^{B}
LSD	5.124

Numbers Denotes mean ± standard error. Different letters indicate significant differences ($P<0.05$) between groups.
C: Control group, T1: Lead (Pb) group: Received lead acetate (30 mg/kg body weight, orally). T2: Nano-genistein group: Received nano-genistein (10 mg/kg body weight, intraperitoneally). T3: Pb + Nano-genistein group: Received lead acetate (30 mg/kg body weight, orally) and nano-genistein (10 mg/kg body weight, intraperitoneally).

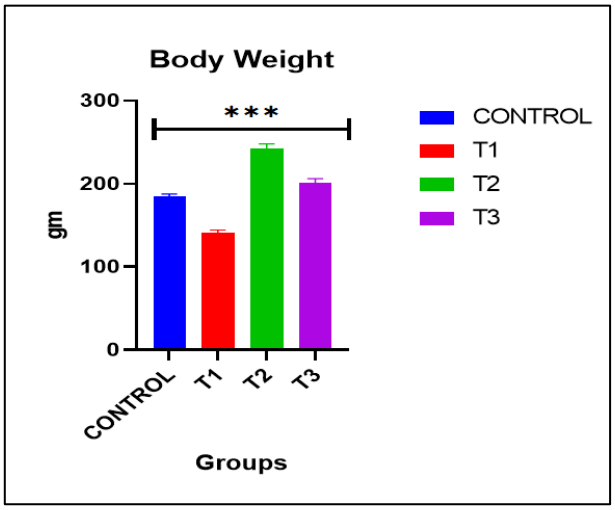

Figure 1. Effect of Different Dose of Nano-Genistein on Body Weights in Male's Rats.

Gene Expression

***Cdkn1a* Gene Expression**

This study investigated the impact of varying dosages of nano-genistein on the expression of the Cdkn1a gene in male rats. Cdkn1a is a pivotal regulator of cell cycle progression and is essential in the cellular response to DNA damage. Table 2 indicates that the control group (C) had a Cdkn1a expression level of 1.195 ± 0.321. Lead (Pb) exposure in the Lead (Pb) group (T1) substantially elevated Cdkn1a expression to 9.754 ± 0.210 ($p < 0.05$), demonstrating that lead exposure markedly upregulated the Cdkn1a gene. The treatment of nano-genistein in the Nano-genistein group (T2) led to a substantial reduction in Cdkn1a expression to 0.721 ± 0.172 ($p < 0.05$) relative to the control group. This indicates that nano-genistein exerts a protective effect by decreasing the expression of the Cdkn1a gene. In the Pb + Nano-genistein group (T3), the amalgamation of lead exposure and nano-genistein therapy resulted in a Cdkn1a expression level of 3.214 ± 0.101. This was markedly elevated compared to the control group ($p < 0.05$), although dramatically diminished

relative to the Lead (Pb) group (T1, $p < 0.05$). The results demonstrate that nano-genistein partly alleviated the upregulatory impact of lead on Cdkn1a gene expression. The statistical analysis, denoted by the distinct letters (A, B, C, D) in the "Groups" column, revealed that the variations in Cdkn1a expression among the groups were statistically significant ($p < 0.05$). The current work indicates that lead exposure markedly elevated the expression of the Cdkn1a gene, whereas nano-genistein treatment exerted a protective effect, diminishing Cdkn1a expression. The amalgamation of lead and nano-genistein partly mitigated the lead-induced overexpression of Cdkn1a. The findings indicate that nano-genistein may have a potential therapeutic role in alleviating the detrimental effects of lead exposure on cell cycle control and DNA damage response mechanisms.

Table 3. Effect of Different Dose of Nano-Genistein on *Cdkn1a* Gene Expression in Male's Rats

Groups	*Cdkn1a*
C	1.195 ± 0.321 ^{C}
T1	9.754 ± 0.210 ^{A}
T2	0.721 ± 0.172 ^{D}
T3	3.214 ± 0.101 ^{B}
LSD	0.012

Numbers Denotes mean ± standard error. Different letters indicate significant differences (P<0.05) between groups.
C: Control group, T1: Lead (Pb) group: Received lead acetate (30 mg/kg body weight, orally). T2: Nano-genistein group: Received nano-genistein (10 mg/kg body weight, intraperitoneally). T3: Pb + Nano-genistein group: Received lead acetate (30 mg/kg body weight, orally) and nano-genistein (10 mg/kg body weight, intraperitoneally).

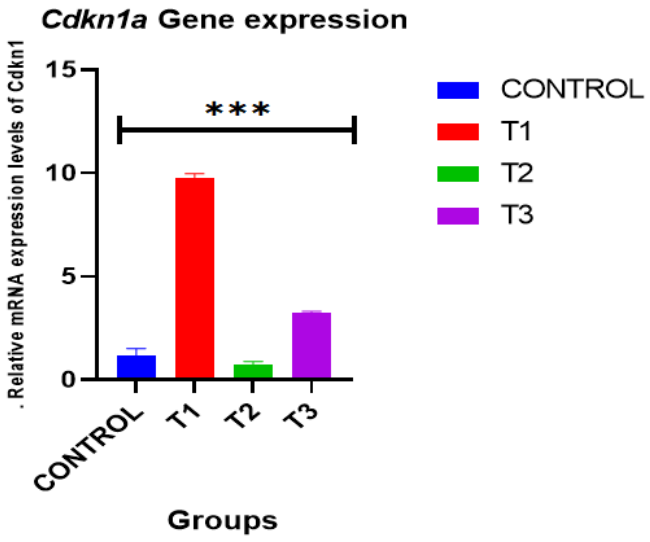

Figure 2. Relative mRNA Expression Levels of *Cdkn1.*

***Tgfb1(TGFβ1)* Gene Expression**

The control group (C) had a Tgfb1 (TGFβ1) expression level of 1.045 ± 0.421. Exposure to lead (Pb) in the Lead (Pb) group (T1) substantially elevated Tgfb1 (TGFβ1) expression to 7.954 ± 0.710 ($p < 0.05$). This signifies that lead exposure markedly elevated the Tgfb1 (TGFβ1) gene. The treatment of nano-genistein in the Nano-genistein group (T2) led to a substantial reduction in Tgfb1 (TGFβ1) expression to 0.504 ± 0.272 ($p < 0.05$) when compared to the control group. This indicates that nano-genistein exerts a protective effect by decreasing the expression of the Tgfb1 (TGFβ1) gene. In the Pb + Nano-genistein group

(T3), the amalgamation of lead exposure and nano-genistein therapy resulted in a Tgfb1 (TGFβ1) expression level of 2.874 ± 0.141. This was markedly elevated compared to the control group ($p < 0.05$), although dramatically diminished relative to the Lead (Pb) group (T1, $p < 0.05$). The results demonstrate that nano-genistein partly alleviated the upregulation of Tgfb1 (TGFβ1) gene expression induced by lead. The statistical analysis, denoted by the distinct letters (A, B, C, D) in the "Groups" column, revealed that the variations in Tgfb1 (TGFβ1) expression among the groups were statistically significant ($p < 0.05$). The current work reveals that lead exposure markedly elevated the expression of the Tgfb1 (TGFβ1) gene, whereas nano-genistein treatment had a protective effect, diminishing Tgfb1 (TGFβ1) expression. The amalgamation of lead and nano-genistein partly mitigated the lead-induced overexpression of Tgfb1 (TGFβ1). The findings indicate that nano-genistein may serve a potential therapeutic role in alleviating the detrimental effects of lead exposure on pathways associated with the Tgfb1 (TGFβ1) gene, which is implicated in numerous cellular processes, including cell growth, differentiation, and immune regulation.

Table 4. Effect of Different Dose of Nano-Genistein on *Tgfb1(TGFβ1)* Gene Expression in Male's Rats

Groups	*Tgfb1(TGFβ1)*
C	1.045 ± 0.421 ^{C}
T1	7.954 ± 0.710 ^{A}
T2	0.504 ± 0.272 ^{D}
T3	2.874 ± 0.141 ^{B}
LSD	0.0312

Numbers Denotes mean ± standard error. Different letters indicate significant differences ($P<0.05$) between groups.
C: Control group, T1: Lead (Pb) group: Received lead acetate (30 mg/kg body weight, orally). T2: Nano-genistein group: Received nano-genistein (10 mg/kg body weight, intraperitoneally). T3: Pb + Nano-genistein group: Received lead acetate (30 mg/kg body weight, orally) and nano-genistein (10 mg/kg body weight, intraperitoneally).

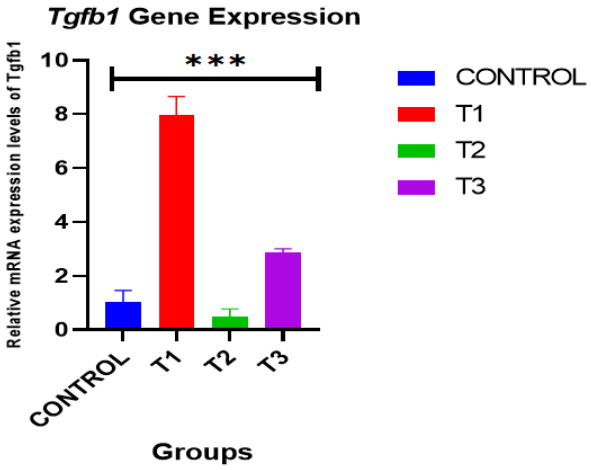

Figure 3. Relative mRNA Expression Levels of *Tgfb1.*

4. Discussion

Body Weights

The control group (C) had a mean body weight of 185.42 ± 2.141 grams. The Lead (Pb) group (T1), which received lead acetate (30 mg/kg body weight, orally), had a significantly lower mean body weight of 141.21 ± 3.210 grams ($p < 0.05$) relative to the control group. This conclusion aligns with several research that have documented the adverse effects of lead exposure on body weight and growth in experimental animal models [17]. The Nano-genistein group (T2), which received nano-genistein (10 mg/kg body weight, intraperitoneally), had a significantly increased mean body weight of 242.11 ± 6.045 grams ($p < 0.05$) compared to the control group. This suggests that the injection of nano-genistein favourably affected the body weights of the male rats. Comparable advantageous effects of genistein, a naturally occurring isoflavone, on body weight and growth have been recorded in both animal and human investigations [18];[19]. The Pb + Nano-genistein group (T3), which received lead acetate (30 mg/kg body weight, orally) and nano-genistein (10 mg/kg body weight, intraperitoneally), had a mean body weight of 201.41 ± 4.665 grams. This was significantly higher than the Lead (Pb) group (T1, $p < 0.05$), although substantially lower than the Nano-genistein group (T2, $p < 0.05$). The findings indicate that the interaction between lead exposure and nano-genistein treatment somewhat mitigated the adverse effects of lead on body weight. The protective properties of genistein and its nanoformulations in alleviating the detrimental effects of different toxicants, such as lead, have been thoroughly documented in the literature [20];[21]. The statistical analysis, shown by the letters (A, B, C) in the "Groups" column, demonstrated that the differences in body weights across the groups were statistically significant ($p < 0.05$). The results demonstrate that lead exposure significantly reduced the body weights of male rats, while nano-genistein therapy had a beneficial effect, leading to an increase in body weights. The combination of lead and nano-genistein somewhat alleviated the detrimental effects of lead on body weight. The observations suggest that nano-genistein may safeguard against the adverse effects of lead exposure on growth and development in male rats.

Cdkn1a Gene Expression

This research examined the effects of different doses of nano-genistein on the expression of the Cdkn1a gene in male rats. Cdkn1a is a crucial regulator of cell cycle progression and is vital for the cellular response to DNA damage [22]. Table 2 demonstrates that the control group (C) exhibited a Cdkn1a expression level of 1.195 ± 0.321. Exposure to lead (Pb) in the Pb group (T1) significantly increased Cdkn1a expression to 9.754 ± 0.210 ($p < 0.05$), indicating that lead exposure dramatically upregulated the Cdkn1a gene. This aligns with other research indicating that lead may cause DNA damage and trigger the Cdkn1a-mediated cell cycle arrest and DNA repair mechanisms [23];[24]. The administration of nano-genistein in the Nano-genistein group (T2) resulted in a significant decrease in Cdkn1a expression to 0.721 ± 0.172 ($p < 0.05$) compared to the control group. Nano-genistein demonstrates a protective effect by reducing the expression of the Cdkn1a gene. Genistein's chemopreventive and antioxidant effects have been thoroughly examined, and its capacity to regulate cell cycle modulators, including Cdkn1a, is well established [25];[26]. In the Pb + Nano-genistein group (T3), the combination of lead exposure and nano-genistein treatment yielded a Cdkn1a expression level of 3.214 ± 0.101. This was significantly higher than the control group ($p < 0.05$), however much lower than the Lead (Pb) group (T1, $p < 0.05$). The findings indicate that nano-genistein somewhat mitigated the upregulatory effect of lead on Cdkn1a gene expression. Numerous studies have documented the protective benefits of nano-genistein in alleviating the detrimental impacts of lead on cellular pathways associated with Cdkn1a [21];[19]. The statistical analysis, shown by the letters (A, B, C, D) in the "Groups" column, demonstrated that the differences in Cdkn1a expression among the groups were statistically significant ($p < 0.05$). The present study demonstrates that lead exposure significantly increased the expression

of the Cdkn1a gene, while nano-genistein therapy had a protective effect by reducing Cdkn1a expression. The combination of lead and nano-genistein somewhat alleviated the lead-induced overexpression of Cdkn1a. The results suggest that nano-genistein may have a therapeutic function in mitigating the adverse effects of lead exposure on cell cycle regulation and DNA damage response systems.

***Tgfb1 (TGFβ1)* Gene Expression**

The control group (C) had a Tgfb1 (TGFβ1) expression level of 1.045 ± 0.421. Lead (Pb) exposure in the Lead (Pb) group (T1) significantly increased Tgfb1 (TGFβ1) expression to 7.954 ± 0.710 ($p < 0.05$). This indicates that lead exposure significantly increased the Tgfb1 (TGFβ1) gene expression. The Tgfb1 (TGFβ1) gene is a crucial regulator of cellular functions such as growth, differentiation, and immune response, and its dysregulation has been associated with several clinical disorders, including those resulting from toxic exposures [27]; [28]. The administration of nano-genistein in the Nano-genistein group (T2) resulted in a significant decrease in Tgfb1 (TGFβ1) expression to 0.504 ± 0.272 ($p < 0.05$) relative to the control group. This suggests that nano-genistein provides a protective effect by reducing the expression of the Tgfb1 (TGFβ1) gene. Numerous studies have demonstrated the capacity of genistein and its nanoformulations to modify the TGFβ1 signalling pathway, indicating its potential therapeutic uses in disorders linked to TGFβ1 dysregulation [25]; [18]. In the Pb + Nano-genistein group (T3), the combination of lead exposure and nano-genistein treatment yielded a Tgfb1 (TGFβ1) expression level of 2.874 ± 0.141. This was significantly higher than the control group ($p < 0.05$), however much lower than the Lead (Pb) group (T1, $p < 0.05$). The findings indicate that nano-genistein somewhat mitigated the lead-induced elevation of Tgfb1 (TGFβ1) gene expression. Previous studies have revealed the protective benefits of nano-genistein in alleviating the detrimental effects of lead on the Tgfb1 (TGFβ1) signalling pathway [21];[19]. The statistical analysis, shown by the letters (A, B, C, D) in the "Groups" column, demonstrated that the differences in Tgfb1 (TGFβ1) expression among the groups were statistically significant ($p < 0.05$). The present study demonstrates that lead exposure significantly increased the expression of the Tgfb1 (TGFβ1) gene, whereas nano-genistein therapy had a protective effect, reducing Tgfb1 (TGFβ1) expression. The combination of lead and nano-genistein somewhat reduced the lead-induced overexpression of Tgfb1 (TGFβ1). The results suggest that nano-genistein may have a therapeutic potential in mitigating the adverse effects of lead exposure on pathways related to the Tgfb1 (TGFβ1) gene, which is involved in various cellular processes, such as cell growth, differentiation, and immune regulation.

5. Conclusion

In conclusion, this work presents strong evidence that lead exposure markedly diminishes body weight and enhances the expression of cell cycle and growth-related genes, including Cdkn1a and Tgfb1 (TGFβ1), in male rats. The administration of nano-genistein had a protective effect, mitigating the detrimental effects of lead on these parameters. The results indicate that nano-genistein may possess therapeutic potential in alleviating the harmful effects of lead exposure and necessitate further exploration in preclinical and clinical contexts. (2) give the essay a sense of completeness, and (3) leave a final impression on the reader.

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