ORIGINAL ARTICLE

Induction of Apoptosis in Male Wistar Rats (Rattus Norvegicus) Exposed to Varying Concentrations of Spodumene

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Abstract

Background: Spodumene, a lithium-rich mineral used in various industrial applications, has raised concerns about its potential toxicity. Cell viability is the ability of a cell to maintain its structural and functional integrity, while apoptosis is a programmed cell death. It is a regulated process essential for maintaining tissue homeostasis.
Methods: This study investigated the cytotoxic effects of spodumene collected from a spodumene mining site at Kakafu village, Lade District, Patigi Local Government Area in Kwara state, Nigeria. Male Wistar rats (Rattus norvegicus) weighing 150g – 250g were exposed to various concentrations (50mg/kg, 100mg/kg, 200mg/kg and 400mg/kg) of spodumene for twenty-eight (28) days. A group that served as the control group was not exposed. Body weights of the animals were evaluated every seven days, while blood samples were obtained at the end of twenty-eight days for analysis of cell viability and apoptosis.
Results: The result of this study revealed that exposure to spodumene did not negatively affect the animals' body weights. However, exposure to spodumene significantly reduced cell viability and induced apoptosis in a concentration-dependent manner. Viable cells and apoptotic cells in the 50 mg/kg concentration were 94.15±0.15 % and 44.75±0.25 % respectively, while viable cells decreased to 86.00±1.00 % and apoptotic cells increased to 86.25±0.25 % in the 400 mg/kg concentration.
Conclusion: In conclusion, the outcome of the study suggests that exposure to spodumene causes cellular toxicity in male Wistar rats. Therefore, there is the need for further research on its safety and potential health risks especially for wild fauna, miners, other workers and people living in close proximity to the mining site.

Keywords: Lithium Compound; Cell Survival, Apoptosis; Rats; Cytotoxicity

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INTRODUCTION

Spodumene belongs to the pyroxene family [1], a lithium-rich mineral with the chemical formula LiAl (SiO3)2, and it is also known as lithium aluminum silicate [2]. The lithium extracted from spodumene is used in manufacturing of ceramics, glass, lithium-ion batteries, and rechargeable lithium batteries [3-5]. These batteries power various modern technologies, including electric vehicles [6], mobile devices [7], and renewable energy systems [8]. Lithium also has medical use in the treatment of bipolar disorder [9,10], reduction of painful cluster headaches [11], decrease in inflammation [12], and reduction of associated autonomic symptoms in humans [13].

Studies have shown that spodumene has various effects on biological systems. Mechanisms of cell death, including apoptosis and necrosis, can be induced by exposure to spodumene [14]. Liu et al. [15] aver that silicon dioxide nanoparticles, a component of spodumene, decrease ATP production, leading to cellular dysfunction. Additionally, spodumene has been associated with immunosuppression, thus resulting in increased susceptibility to infections [16].

Prolonged exposure to spodumene has been shown to reduce cell viability which is the ability of cells to maintain their structural and functional integrity [17] in various cell types [18], accompanied by adverse health effects such as nausea, vomiting, diarrhea, abdominal pain, and even coma or death [19]. Assays for cell viability provide essential

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insights into cellular responses to various stimuli and are critical for assessing cytotoxic effects of substances (17, 20]. It is worthy of note that exposure to spodumene has been reported to decrease cell viability through oxidative stress and inflammation [18, 21].

In the control of cell populations, apoptosis is considered as a normal event [22]. However, it can be induced by toxicants that will reduce the cell population. Thus, it is a programmed cell death, which is a regulated process essential for maintaining tissue homeostasis [23]. Spodumene has been reported to cause oxidative stress and inflammation in mice, which are key triggers of apoptotic pathways [18]. While apoptosis increases in rat bone marrow cells as a result of spodumene exposure [15], oxidative stress damages cellular components, including DNA, proteins, and lipids, and inflammation, in turn, induces apoptosis through the activation of pro-inflammatory cytokines and chemokines [19, 21].

Chen et al. [24] investigated spodumene's effects on gene expression related to cell cycle regulation in male Wistar rats and observed significant changes that indicate cell cycle dysregulation which can trigger apoptotic pathways. Gao et al. [25] demonstrated spodumene-induced apoptosis in rat blood cells, mediated by the activation of caspase-3 and caspase-9, key enzymes in the apoptotic pathway. However, limited studies have explored the mechanisms by which spodumene causes oxidative stress and apoptosis in mammals at environmentally relevant exposure levels. Thus, there is a significant gap in the literature regarding its specific effects on cell viability and apoptosis, particularly in male Wistar rats. Even though most previous studies have focused on spodumene's industrial significance, its role as a lithium source, and its broader toxicological effects, the mechanisms underlying spodumene-induced cellular responses, including programmed cell death (apoptosis) and changes in cell viability are not well understood.

Disruption in the regulatory function of apoptosis is closely associated with various diseases, including cancer, autoimmune disorders, and neurodegenerative conditions such as Alzheimer's and Parkinson's disease. Apoptosis, or programmed cell death, is a fundamental process that maintains cellular homeostasis by eliminating damaged or unnecessary cells. Any imbalance in this process—whether excessive or insufficient apoptosis—can contribute to pathological conditions. Similarly, cell viability refers to the proportion of live, healthy cells within a given population [26], and this serves as a crucial indicator of overall cellular health, metabolic activity, and response to environmental stressors. It is a common practice in toxicology and pharmacology to evaluate the effects of various substances on cell populations.

The mining of spodumene in Kakafu village raises concerns about its potential cytotoxic effects on both the environment and human health. Wild mammals inhabiting the area as well as miners and workers, directly or indirectly exposed to spodumene, may be at risk due to prolonged contact with spodumene dust or runoff contamination. Despite the increasing industrial significance of spodumene as a primary lithium source, there is limited information on its toxicological effects, particularly from this specific mining site. Therefore, this study was conducted to investigate the effects of exposure to spodumene from the Kakafu mining site on apoptosis and cell viability in male Wistar rats.

METHODS

Collection and preparation of spodumene samples

Spodumene was collected from Kakafu village, located in Lade District, Patigi Local Government Area of Kwara State, Nigeria. Kakafu village is located on latitude 9º30` North of the Equator and longitude 4º48` East of the Greenwich Meridian.

The spodumene samples were ground into fine powdery form with a porcelain mortar and pestle in the laboratory. The finely powdered samples were sieved with a 2-micrometer mesh to obtain fine particles which easily dissolved in water.

Experimental male Wistar rats

Thirty-five adult male Wistar rats (Rattus norvegicus) aged about 240 days, and weighing about 150 – 240g each were used for this study. The animals were purchased from the Department of Biochemistry, University of Ilorin, Ilorin, Nigeria. The animals were housed and kept in clean and well-ventilated cages in the animal house of the Department of Zoology, University of Ilorin. They were fed ad libitum and given clean water to drink. They were maintained at a 12 h/12 h light/dark cycle. The rats were acclimatized to the laboratory conditions for a period of fourteen (14) days. Handling of the rats was done according to the strict guidelines and regulations of the Animal House Section of the Department of Zoology, University of Ilorin, Kwara State, Nigeria. The experiments were carried out in accordance with the US National Research Council Committee's care and use of laboratory animals [27] and UK guidance of the operation of animals (Scientific Procedures) Act, 1986, with amendment regulations 2012 (SI 2012/3039) [28].

Animal groups and exposure

The rats (n = 35) were randomly divided into five groups (groups 1-5) of seven rats per group. Group one was the control group with no exposure to spodumene. Groups two, three, four and five were administered 50 mg/Kg, 100 mg/kg, 200 mg/kg and 400 mg/kg spodumene respectively via oral gavage for 28 days.

Body weights of the animals

The body weights of the rats were measured before the administration of spodumene in the first week, and measured weekly over the 28-day exposure period. The

weights were taken every seven days, making four times during the exposure period: Weeks 1, 2, 3 and 4.

Blood sample collection process

The rats were anesthetized using chloroform to minimize stress and discomfort. Blood samples were collected afterward from the tail vein using a sterile syringe and needle. The blood samples for apoptosis and cell viability analysis were collected in heparinized tubes.

Cell viability analysis

Blood sample collected into heparinized tubes was centrifuged at 1,500 rpm for 5 minutes [29]. About 20 µL of the blood sample supernatant was added to a 96-well plate and incubated at room temperature for 5 minutes. After 5 minutes, 8.5 µL of trypan blue (0.2%) was added and mixed using a micropipette. From the mixture, 10 µL was pipetted and released gently on a clean glass slide. Before imaging, a glass coverslip was placed gently on each slide and sealed with nail polish. Fluorescence microscope (Olympus BX51) at 10x magnification was used to image each slide. Viable cells (%) were calculated using the following formula:

Viable cells = (total number of viable cells)/(total number of cells) x 100

Cell death analysis

Blood sample collected into heparinized tubes was centrifuged at 1,500 rpm for 5 minutes [29]. About 20 µL of the blood sample supernatant was added to a 96-well microplate and incubated at room temperature for 5 minutes. After 5 minutes, 1% of Acridine Orange was added and mixed using a micropipette. From the mixture, 10 µL was pipetted and released gently on a clean glass slide. Before imaging, a glass coverslip was placed gently on each slide and sealed with nail polish. A fluorescence microscope (Olympus BX51) at 10x magnification was also used to image each slide. Apoptotic cells (%) were calculated using the following formula:

Apoptotic cells = (total number of apoptotic cells)/(total number of cells) x 100

Statistical analysis

The mean and standard error of means of animal weights and apoptotic cells were analyzed using Statistical Package for Social Sciences (SPSS) version 21. Analysis of Variance (ANOVA) was used to test for variations among the values while Posthoc test [Duncan Multiple Range Test (DMRT)] was used to test for significant differences among the means of the control and the treatment groups at $p<0.05$. Microsoft Excel 2021 was used for all graphical illustrations.

RESULTS

Spodumene affects the body weight of male Wistar rats

The mean and standard deviation of the body weight of the male Wistar rats of several groups are shown in Table 1. The data revealed significant variations within and across the five groups of male Wistar rats used in the study.

The results from the body weight analysis indicate that exposure to spodumene positively affected the body weight of the male Wistar rats, with significant differences observed in the weight trends over the 28-days period between the control and treatment groups.

Spodumene reduces cell viability in male Wistar rats

The rats exposed to 400 mg/kg of spodumene had the lowest recorded viable cells (86.00 ± 1.00 %) while the rats exposed to 50 mg/kg of spodumene had highest recorded viable cells (94.15 ± 0.15 %). The mean viable cells of the control group was (97.30 ± 0.30 %) (Table 2).

The result shows the outcome of the comparison of cell viability levels between control group and rats treated with increasing concentrations of spodumene. One-way Analysis of Variance (ANOVA) indicated that the viable cells observed in the group exposed to 50mg/kg and 100mg/kg of spodumene were not significantly different from one another while there was a significant difference between the control and group treated with 200mg/kg and 400mg/kg at $p<0.05$. Duncan's Multiple Range Test also confirmed the significant difference.

Spodumene induces cell death in male Wistar rats

The rats exposed to 400 mg/kg of spodumene had the highest recorded apoptotic cells (86.25 ± 0.25 %) while the rats exposed to 50 mg/kg of spodumene had the lowest recorded apoptotic cells (44.75 ± 0.25 %). The apoptotic cells of the control group had the mean of (23.00 ± 0.50 %) (Table 3). The induction of apoptotic cells was concentration-dependent (Figure 1).

Table 1. Body weights of male Wistar rats exposed to different concentrations of spodumene

Week	Control	50mg/kg	100mg/kg	200mg/kg	400mg/kg
	Mean ± SEM	Mean ± SEM	Mean ± SEM	Mean ± SEM	Mean ± SEM
1	179.86±27.36	156.43±51.37	172.43±38.57	191.43±29.43	181.57±28.98
2	186.57±29.63	169.57±37.78	177.33±50.17	195.00±34.61	182.14±29.54
3	196.29±29.96	194.71±33.66	185.71±29.12	199.50±32.37	189.29±29.93
4	206.00±28.25	201.00±38.39	206.33±33.73	202.17±26.80	192.71±35.98

SEM: The standard error of the mean

Table 2. Cell viability of the blood of male Wistar rats exposed to different concentrations of spodumene

Treatments	Cell Viability Mean ± SEM (%)
Control	97.30 ± 0.30[a]
50mg/kg	94.15 ± 0.15[b]
100mg/kg	93.55 ± 0.35[b]
200mg/kg	88.85 ± 0.85[c]
400mg/kg	86.00 ± 1.00[d]

SEM: the standard error of the mean.
Superscript indicates statistical significance at $P < 0.05$.
Superscript with the same alphabets indicates no significant difference

Table 3. Apoptosis observed in the blood of male Wistar rats exposed to different concentrations of spodumene

Treatments	Apoptosis Mean ± SEM (%)
Control	23.00 ± 0.50[a]
50mg/kg	44.75 ± 0.25[b]
100mg/kg	47.00 ± 0.50[c]
200mg/kg	62.30 ± 0.50[d]
400mg/kg	86.25 ± 0.25[e]

SEM: the standard error of the mean. Superscript indicates statistical significance at $P < 0.05$. Superscript with the same alphabets indicates no significant difference

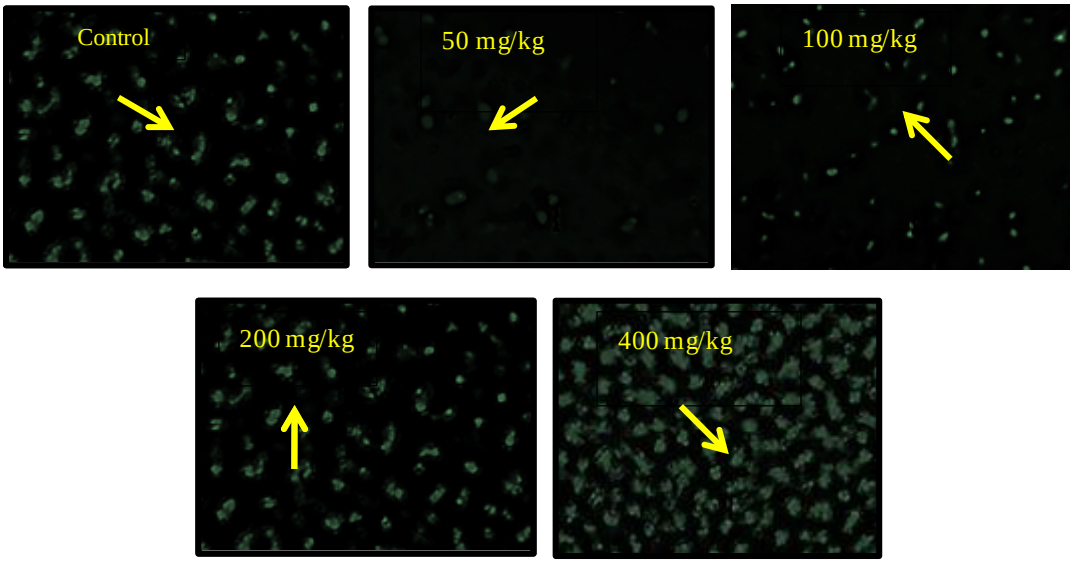

Figure 1. Apoptosis observed in rats exposed to different concentrations of spodumene

One-way Analysis of Variance (ANOVA) indicates that the rate of apoptosis observed in all the spodumene-exposed groups was significantly different from one another at $p<0.05$. Duncan's Multiple Range Test also confirms the significant difference at $p<0.05$.

DISCUSSION

The study on spodumene-induced cytotoxicity in male Wistar rats (Rattus norvegicus) was conducted to expand knowledge on the effects of spodumene exposure and its potential toxicity. The findings showed a steady weight increase across all experimental groups. These results diverge from previous studies on lithium compounds, which have largely reported either weight loss or no significant changes in body weight [30, 31]. The observed weight increase in this study suggests a dose-dependent effect, where higher spodumene exposure correlates with greater weight gain.

One possible explanation for this weight gain is spodumene's lithium content and its influence on metabolic pathways that regulate energy homeostasis. Lithium has been reported to affect glycogen synthesis, glucose metabolism, and insulin signaling, which may contribute to changes in weight [32, 33]. These metabolic effects suggest that spodumene may alter adipogenesis, possibly leading to increased fat deposition or changes in appetite-regulating hormones such as leptin and ghrelin [34].

The observed increase in apoptosis was directly proportional to the concentration of treatment given. This means that the concentration of the spodumene treatment increased, apoptosis also increased. Conversely, the decrease in cell viability was inversely proportional, that is, as spodumene treatment decreased, cell viability decreased. The increased apoptosis and reduced cell viability in spodumene-treated rats may be attributed to effects of spodumene on hematopoietic stem cells as observed by Li and Wang [34]. Patel et al [35] reported that spodumene inhibits granulocyte-macrophage colony-stimulating factor (GM-CSF), leading to reduced cell proliferation and increased apoptosis. Additionally, increase in the apoptotic cells and reduction in viable cells recorded across the groups are consistent with positions held in previous studies that have shown oxidative stress-inducing properties of spodumene which may contribute to cellular damage and apoptosis [36]. Although, a study by Geddes et al. [37] found no significant changes in apoptosis and cell viability in spodumene-treated rats. Another study by McKnight et al [38] reported that lithium, a major component of spodumene actually increased viable cell count in hematopoietic stem cells. These discrepancies may be attributed to differences in experimental design, dosage, or species of organism used.

The reduced cell viability in spodumene-treated rats may also be attributed to effects of spodumene on cellular metabolism. Spodumene has been shown to inhibit glycolysis and reduce ATP production, leading to cellular energy depletion [36]. The increased apoptosis and reduced cell viability observed in this study may be related to lithium's pharmacological mechanism of action. Lithium's ability to inhibit inositol monophosphatase and modulate G-protein coupled receptor signalling may contribute to its cytotoxic effects [39]. Moreover, the effects of spodumene on hematopoietic stem cells may have long-term consequences for hematopoiesis. The reduced self-renewal capacity and increased apoptosis of hematopoietic stem cells may thus lead to reduced cell viability observed in this study. This may also be attributed to impact of spodumene on cellular metabolism. Research has shown that spodumene inhibits glycolysis and reduces ATP production, leading to cellular energy depletion and metabolic stress [40]. Moreover, lithium's known pharmacological effects such as its ability to inhibit inositol monophosphatase and modulate G-protein coupled receptor (GPCR) signalling may contribute to its cytotoxic properties [41].

Long-term spodumene exposure may also affect hematopoiesis, as indicated by the reduced self-renewal capacity of hematopoietic stem cells. This could lead to hematopoietic insufficiency and increased susceptibility to haematological disorders, such as anaemia, leukopenia, or myelodysplastic syndromes [42].

LIMITATIONS

1. Species-Specific Responses: The study was conducted using male Wistar rats, which may not fully represent the effects of spodumene exposure in other species, including humans. Differences in metabolic pathways and cellular responses could yield varying results.
2. Short-Term Exposure Duration: The study primarily examined acute exposure, whereas chronic exposure studies are needed to determine long-term effects, including cancer risk and systemic toxicity.
3. Limited Dose Range: The study focused on a specific range of spodumene concentrations, but effects at lower or higher doses remain unexplored. A dose-response curve analysis would provide a more comprehensive toxicity profile.
4. Lack of Biomarker Analysis: While apoptosis and cell viability were assessed, further analyses of oxidative stress markers (e.g., MDA, SOD, GSH) and inflammatory cytokines (e.g., TNF-α, IL-6) could provide deeper mechanistic insights.
5. Environmental and Occupational Exposure Scenarios: The study used controlled laboratory conditions, which may not fully replicate real-world exposure scenarios experienced by miners, workers, and local wildlife in Kakafu village.

CONCLUSION

Given the reported findings, the deduction from the study is that spodumene treatment enhances apoptosis in male Wistar rats while inhibiting viability of cells at the same time. This is an indication of potential cytotoxicity of spodumene. Therefore, there is health risk potentials for wild mammals, miners and other workers at Kakafu spodumene mining site. Meanwhile there is the need for further research to develop appropriate and safety guidelines of the mining of spodumene. In that wise, the fauna in the wild will be preserved and the health of miners, other workers and people close to the site will not be put to risk.

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