Multitech Journal of Science and Technology (MJST)
Vol.2, No.6, 2025:379-388

Histopathological Evaluation of the Effect of Dextromethorphan and Guaifenesin on the Lung And Kidney Tissues in Albino Rats

Momodu[1*], Oseni Akhere[2], Iyare Godfrey Innocent[3], Avwioro Godwin Ovie[4]
[1,2,3]Edo State University
[4]Delta State University
Corresponding Author: Momodu o_momodu@yahoo.com

A R T I C L E I N F O

Keywords: Histopathological Evaluation, Effect, Guaifenesin, Kidney Tissues

Received : 3 April
Revised : 20 May
Accepted: 20 June

A B S T R A C T

Dextromethorphan and guaifenesin are two commonly used medications for the treatment of cough and colds. While their efficacy in alleviating respiratory symptoms is well documented, comprehensive data on their histopathological impact on vital organs is limited. This study determined the effect of the drugs on the lungs and kidney tissues of Albino rats. Twenty four adult albino rats weighing 110±20g were grouped into 4, of 6 rats each. Group A received only normal feed and water daily and served as the control. Groups B, C and D were administered with 0.1ml, 0.5ml and 1ml respectively with oral dextromethorphan and guaifenesin for 28 days. Blood was collected into lithium heparin for biochemical analysis, while the liver and kidney tissues were fixed in 10% formol saline, processed by the paraffin wax method and stained with H&E for examination. Biochemical analysis showed no significant changes in the values of total protein, albumin and Malondialdehyde, while there was a reduction in the values globulin from 8.10 ± 0.59 to 3.85 ± 2.56, glutathione increased from 112.64 to 462.03 ± 1.88 in the low and high doses. Histological findings showed no significant alterations in lungs and kidney tissues

DOI: https://doi.org/10.59890/k1bwvd23
E-ISSN: 3026-2410
https://penerbitjurnalinternasional.com/index.php/mjst/index

INTRODUCTION

The increasing use of Dextromethorphan and guaifenesin, necessitates a deeper exploration of their long-term effects on critical organ systems such as the kidney and the liver. While these medications are effective in symptom management, there is growing evidence that their active components might induce histological changes, potentially compromising the integrity and function of these organs (Gupta and Gupta, 2020). The delicate architecture of lung tissue, essential for efficient gas exchange, may be altered by chronic exposure to these substances, leading to possible respiratory complications (Nigam and Bush, 2019). Similarly, the kidneys, which are involved in metabolizing and excreting these compounds, may experience structural and functional changes that could impair their ability to maintain homeostasis (Bezerra et al.,2023). Dextromethorphan and guaifenesin are commonly used drugs for the treatment of coughs and colds (Farah, 2020). Dextromethorphan is a cough suppressant, while guaifenesin is an expectorant. These drugs are often combined in pharmaceutical products to provide relief from coughs and help clear mucus from the airways, thus helping to clear symptoms associated with respiratory tract infections and colds. (Manti et al., 2020). Dextromethorphan acts primarily on the central nervous system, specifically targeting the medullary cough center in the brain to suppress the cough reflex. It is considered a non-narcotic cough suppressant and is widely available without a prescription in many countries. Its mechanism of action involves blocking NMDA receptors in the brain, which are also associated with pain perception and certain neurological conditions (Eccles, 2020). Though generally considered safe at recommended doses, dextromethorphan has been the subject of misuse, particularly among adolescents due to its dissociative effects at higher doses (Kandiwa et al., 2022). Additionally, some studies have explored its potential use beyond cough suppression, such as in the treatment of neurological disorders (Kandiwa et al., 2022). Guaifenesin is classified as an expectorant and works by increasing the volume and reducing the viscosity of secretions in the respiratory tract. This makes it easier for patients to expel mucus through coughing (Collins et al., 2019).

LITERATURE REVIEW

Guaifenesin has been included in cough formulations for decades and is generally regarded safe with few side effects. Some studies in Asia focused on the potential of guaifenesin to improve patients' outcomes in conditions such as chronic bronchitis and some forms of chronic obstructive pulmonary diseases and (Rouaz et al., 2021) stated that despite its wide use its effectiveness as a standalone expectorant needs more comprehensive work (Lai et al., 2018). Misuse or overuse of the drug can lead to potential side effects or complications, including dependency on certain substances such as codeine (Blenkinsopp et al., 2022).

METHODOLOGY

Animal Model and Handling

Twenty four adult albino rats of comparable sizes and weighing 90g to 130g, 5 weeks old were used in this study. The rats were fed with Growers' mash and water ad libitum. The animals were maintained and utilized in accordance with the standard guide for the care and use of laboratory animals.

Grouping of Animal Model

The experimental animals were separated into four groups (A – D). Each group contains 6 rats (n = 6). Group A served as the positive control, while groups B, C and D serve as tests. The rats had access to feeds and water ad libitum.

LD50 of Dextromethorphan and guaifenesin

The toxicological information on the acute oral toxicity dose of dextromethorphan/guaifenesin in Wistar rats has LD50 to be greater than 1500 mg/kg (>1500 mg/kg) (go.drugbank.com, 2024). Prior to the main study, we carried out an acute toxicity test, using the Lorke method (Lorke, 1983) in which adult male Wistar rats were exposed to 10, 100, 1000, 1600, 2900, and 5000 mg of TLD/kg body weight. The LD50 was found to be <10 mg/kg body weight. Therefore, a dosage below <10 mg/kg was used in the experiment.

Administration of drug

The drug dextromethorphan and guaifenesin was given orally for 28 days and all the animals had access to water and feeds ad libitum.

- Group A served as the control and did not receive the drug.
- Group B was the low dose and had 0.1ml.
- Group C received the average dose of 0.5ml.
- Group D was administered with the high dose of 1ml.

Sample Collection and Analysis

The weights of the animals were measured before and at the end of experiment. The lungs and kidney of each rats were fixed in 10 % formol saline and the whole blood was collected into lithium heparin container for biochemical analysis.

Histological processing

The fixed Lungs and Kidney was taken for histological processing following standard histological procedures that encompassed the following steps; fixation, dehydration, clearing, impregnation, embedding, sectioning, staining and microscopy.

Assessment of lipid Peroxidation

Lipid peroxidation in post mitochondrial fraction was estimated spectrophotometrically by thiobarbituric acid reactive substances (TBARS) method as described by Varshey and Kale (1990).

Determination of Reduced Glutathione (GSH) Level

The method of Beutler *et al*. (1963) was adopted in estimating the level of reduced glutathione (GSH) in some organs of rats treated with hesperidin and 4 vinylcyclohexenediepoxide.

Statistical analysis

The data obtained was expressed as mean ± standard deviation (SD) and analyzed for statistical significance using student t test and one-way ANOVA

followed by LSD test where applicable; all in Statistical Package for Social Sciences (SPSS version 23). $P < 0.05$ will be considered significant. Histological findings were presented in photomicrographs in plates. The results will be presented using suitable tables and micrograph.

RESULTS

Table 1. A Comparative Analysis of Body Weight Changes Across Four Groups: Control (CTRL), High Dose (1ml), Average Dose (0.5ml), and Low Dose (0.1ml) of Cough Syrup.

Group	Initial Body Weight (Mean ± SD)	Final Body Weight (Mean ± SD)	t-value (Equal variances not assumed)	P-value (2-tailed)
CTR)	114.63 ± 21.79	133.10 ± 24.15	-0.983	0.382
High Dose (1ml)	126.67 ± 4.91	156.63 ± 25.39	-2.007	0.174
Average Dose (0.5ml)	117.17 ± 1.33	136.93 ± 1.76	-15.552	<0.001*
Low Dose (0.1ml)	119.90 ± 2.77	131.47 ± 1.12	-6.699	0.010*

P-Value < 0.05 Was Considered Significant

Table 1: In the Control group (CTRL), the mean body weight increased by about 21g, but this change was not statistically significant (t = -0.983, P = 0.382). The high dose group (1ml) showed an increase of about 38g, but the change was also not statistically significant (t = -2.007, P = 0.174). In contrast, the average dose (0.5ml) and low dose (0.1ml) groups exhibited statistically significant changes in body weight, 20g and 12g respectively. (t = -15.552, P < 0.001), with a very small P-value indicating strong evidence against the null hypothesis of no difference. Similarly, the Low Dose group showed a significant increase from 119.90 ± 2.77 to 131.47 ± 1.12 (t = -6.699, P = 0.010).

Table 2. A Comparative Analysis of Protein, Albumin, Globulin, Reduced Glutathione (GSH), Malondialdehyde (MDA), Changes Across Four Groups: Control (CTRL), High Dose (1ml), Medium Dose (0.5ml), and Low Dose (0.1ml) of Cough Syrup

Parameter	Control (Mean ± SD)	Low Dose (Mean ± SD)	Medium Dose (Mean ± SD)	High Dose (Mean ± SD)	F-value	P-value
Total Protein (g/dL)	5.75 ± 0.35	5.67 ± 1.28	4.64 ± 0.32	7.82 ± 2.78	2.537	0.122
Albumin (g/dL)	3.90 ± 1.10	3.23 ± 0.74	2.68 ± 0.17	3.97 ± 0.30	3.443	0.065
Globulin (g/dL)	8.10 ± 0.59	2.45 ± 1.22	1.96 ± 0.46	3.85 ± 2.56	9.151	0.004*
Reduced Glutathione (GSH, µmol/L)	112.64 ± 1.26	416.00 ± 3.73	462.03 ± 1.88	107.47 ± 1.86	291.6	<0.001*

Malondialdehyde (MDA, nmol/mL)	0.83 ± 0.19	±	2.02 ± 1.08	±	2.62 ± 1.17	0.78 ± 0.26	±	3.007	0.087

P-Value < 0.05 was considered significant

The table presents the biochemical parameters evaluated across different treatment groups Control, Low Dose, Medium Dose, and High Dose with corresponding mean values, standard deviations (SD), F-values, and p-values. These parameters include protein, albumin, globulin, reduced glutathione (GSH), and malondialdehyde (MDA) levels, which are markers for nutritional and oxidative stress status. For total protein, levels ranged from 5.75 ± 0.35 g/dL in the control group to 7.82 ± 2.78 g/dL in the high-dose group, showing some variation, though the change was not statistically significant (p = 0.122). Albumin also varied across groups, with the highest level in the high-dose group (3.97 ± 0.30 g/dL) and the lowest in the medium-dose group (2.68 ± 0.17 g/dL), yet this difference was not statistically significant either (p = 0.065). In contrast, globulin levels demonstrated a significant difference across groups (p = 0.004). The control group had the highest globulin value (8.10 ± 0.59 g/dL), while the medium-dose group had the lowest (1.96 ± 0.46 g/dL), indicating a marked dose-related decline. Reduced glutathione (GSH), a key antioxidant, showed a highly significant variation (p < 0.001), with elevated levels in both the low-dose (416.00 ± 3.73 µmol/L) and medium-dose (462.03 ± 1.88 µmol/L) groups compared to the control (112.64 ± 1.26 µmol/L). Lastly, malondialdehyde (MDA), a marker of lipid peroxidation, increased in the low-dose and medium-dose groups (2.02 ± 1.08 and 2.62 ± 1.17 nmol/mL, respectively), compared to the control (0.83 ± 0.19 nmol/mL). However, the difference was not statistically significant (p = 0.087).

Histological Findings

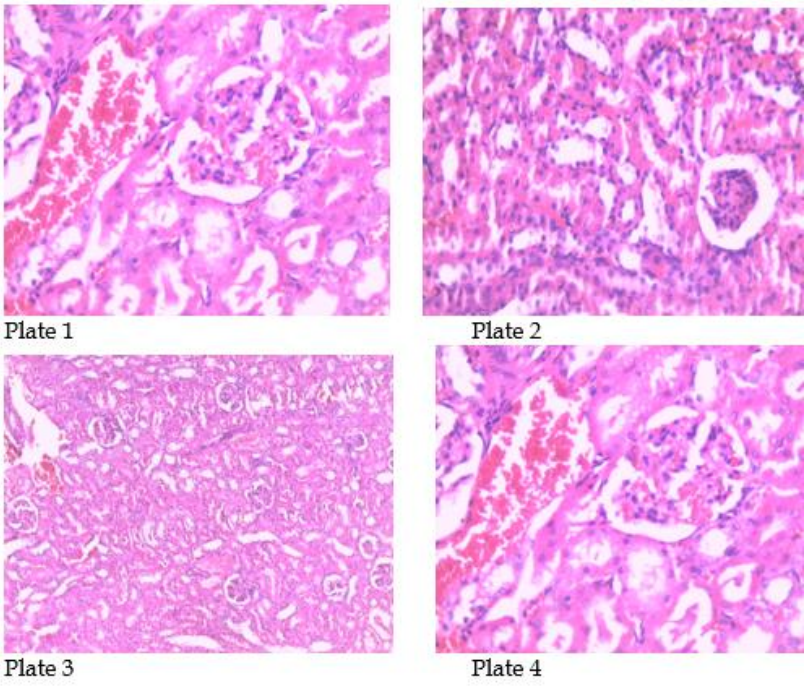

Figure 1. kidney sections from control group and tests showing normal glomerulus, bowman's capsule and renal tubules

Plate 1, 2, 3 and 4: kidney sections from control group and tests showing normal glomerulus, bowman's capsule and renal tubules. H&E (Plate 3 X100), (Plates 1, 3 and 4, X400).

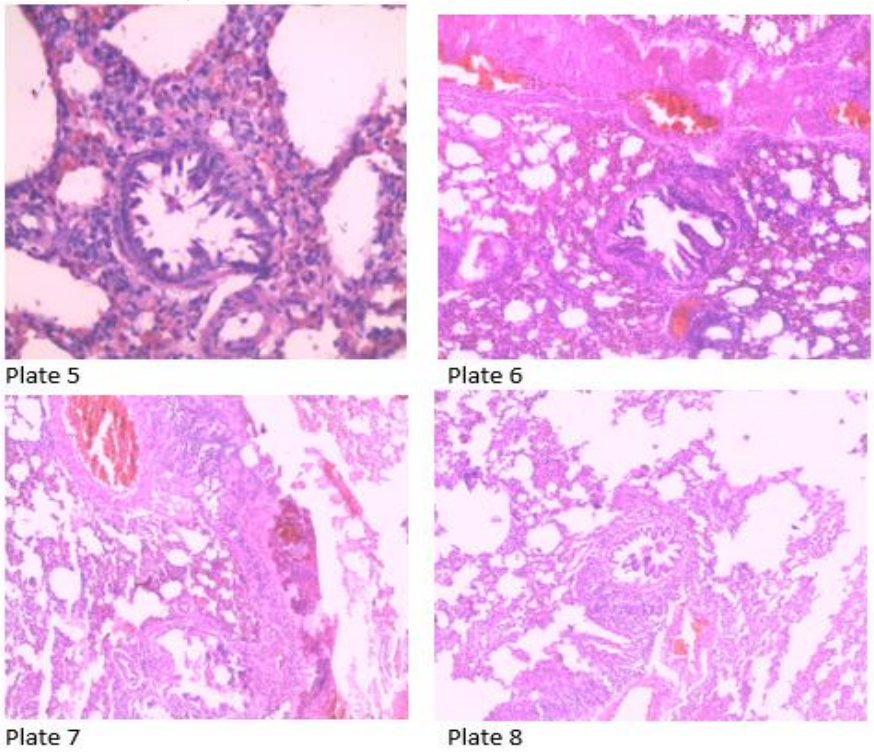

Figure 2. Lungs Tissue Sections From the Control and Test Sections Showing Normal Bronchiole

Plate 5, 6, 7 and 8 are lungs tissue sections from the control and test sections showing normal bronchiole, alveolar sac. No evidence of degenerative changes H&E X400.te 8:

DISCUSSION

Dextromethorphan and Guaifenesin are commonly used together as medication. While both drugs are generally safe at therapeutic doses, their prolonged use or at high doses may pose risks to vital organs of the body. The comparison of initial and final body weights across experimental groups treated with varying doses (low, medium, and high) of the test compound (dextromethorphan and guaifenesin), alongside the control group revealed that the control group exhibited an increase in body weight from 114.63 ± 21.79 g to 133.10 ± 24.15 g, this change was not statistically significant ($p = 0.382$), indicating normal growth over the study period. Similarly, the high-dose group (1 ml) showed a notable weight increase (from 126.67 ± 4.91 g to 156.63 ± 25.39 g), but this too was not significant ($p = 0.174$). In contrast, the average-dose (0.5 ml) and low-dose (0.1 ml) groups recorded statistically significant increases in body weight, with p-values of <0.001 and 0.010, respectively.

These results imply that moderate and low doses of the test compound may have favorable effects on body weight, while higher doses fail to produce significant changes, potentially due to saturation or metabolic adaptations. The findings for the average- and low-dose groups are in agreement with those of

Lund et al., (2024), who found that in rodents, excessive caloric intake or high-fat diets can activate compensatory mechanisms like reduced food intake or increased energy expenditure that blunt further weight gain at higher doses. Similarly, Shallangwa et al., (2025) reported that intermediate dosages of bioactive compounds achieved the most effective weight-modulating outcomes without provoking the adverse reactions often seen with high doses. The observed weight gain at moderate doses may be attributed to improved appetite stimulation, enhanced digestive efficiency, and better nutrient absorption, particularly common with plant-derived or nutraceutical agents, which have been shown to support effective feed utilization and energy retention, ultimately contributing to significant body weight increase.

Cough syrups, particularly those containing active ingredients like dextromethorphan, guaifenesin, and other excipients, can influence biochemical and antioxidant markers depending on dosage and duration of use. Their effects on total protein and albumin levels may arise from hepatic metabolism or mild hepatotoxicity, as the liver is responsible for synthesizing these proteins. Regarding antioxidant markers, such as glutathione (GSH) and malondialdehyde (MDA), cough syrups may induce oxidative stress at higher doses due to metabolic byproducts (Eccles, 2020).

Table 4.2 illustrates the biochemical effects of different doses of the test compound on protein metabolism and oxidative stress indicators in laboratory animals. The outcomes of this research align with those of Chu et al., (2024), whose meta-analysis reported significantly elevated levels of antioxidant enzymes such as GSH-Px and SOD in rodents. In contrast, the results differ from those of Oladipo et al., (2016), which found increased levels of globulin and malondialdehyde (MDA) alongside a reduction in glutathione-associated enzymes. However, it is important to note that Oladipo's study involved exposure to low-dose heavy metals like lead, cadmium, and manganese, which likely account for the contrasting findings. The observed improvement in antioxidant status in the current study could be due to the ability of certain constituents in the test substance to enhance the body's natural antioxidant defense, resulting in higher glutathione production. Additionally, the elevated globulin levels noted here may be a response to inflammatory activity potentially triggered by the administered compound.

The histological findings presented in this study provide important insight into the organ-level safety profile of Dextromethorphan and Guaifenesin in rats, focusing on the lung and kidney tissues. The microscopic examinations, as described in Plates 1 through 8, show no observable degenerative changes in the renal or pulmonary architecture across all treatment groups (Groups A, B, and C), as well as in the control group. This suggests that, under the experimental conditions and dosages used, both Dextromethorphan and Guaifenesin did not induce tissue-level toxicity in these organs. These findings are consistent with earlier reports highlighting the relative safety of these medications at therapeutic levels. For instance, Guaifenesin is widely recognized for its mucolytic action and is not typically associated with organ toxicity (Albrecht et al., 2017). Similarly, according to Liu et al., 2021, dextromethorphan, while occasionally misused, is

considered non-nephrotoxic and significantly attenuates the increase in ROS production when used appropriately.

However, in contrast these results with findings from high-dose or long-term exposure studies. Kayode et al. (2021) reported that supratherapeutic doses of dextromethorphan in rats caused mild histological alterations in renal tissues. Likewise, Okamoto et al. (2025) whose study stated that increased dose of dextromethorphan can lead to serotonin syndrome leading to rhabdomyolysis and dialysis-requiring acute kidney injury in humans. Notably, none of these pathological changes were observed in the present study, indicating that dose and duration are likely key factors influencing toxicity outcomes.

In terms of pulmonary effects, Lu et al. (2022) noted that Long course of low-dose dexamethasone was able to impressively improve pulmonary fibrosis. In similarity, the lung tissue sections in this study show preserved bronchiole and alveolar architecture, with no vascular congestion or cellular degeneration, reinforcing the view that controlled, long-term use of these agents is unlikely to compromise respiratory tissue integrity. Moreover, these findings support the conclusion by Ohar et al. (2019), whose study stated that Guaifenesin can be used for the treatment of stable chronic bronchitis further solidifying the safe usage of Guaifenesin on the lungs.

CONCLUSIONS AND RECOMMENDATIONS

In conclusion, this study assessed the histopathological effects of dextromethorphan and guaifenesin on the lung and kidney tissues of albino rats. The results revealed that both organs maintained normal histological architecture across all treatment groups, indicating no observable structural damage or toxicity under the conditions studied. In addition to the preserved tissue integrity, a statistically significant increase in globulin and reduced glutathione (GSH) levels was observed. The rise in globulin suggests a possible immunomodulatory effect, while the elevated GSH levels reflect an enhancement of the antioxidant defense system. These findings suggest that, at the administered doses, dextromethorphan and guaifenesin do not produce adverse morphological effects on lung and kidney tissues and may even support immune and antioxidant functions, warranting further investigation into their systemic safety and potential therapeutic benefits.

FURTHER STUDY

This study still has limitations so further research is needed on the topic of Histopathological Evaluation of the Effect of Dextromethorphan and Guaifenesin on the Lung and Kidney Tissues to perfect this study and increase insight for readers and authors.

ACKNOWLEDGMENT

Authors appreciate the technical contributions of Mr Wisdom Ohiwerei and Mr Michael Otaye for their immense contributions and supports. This research was self-funded and did not receive any grants from funding agencies in the public, private or non- profit organizations.

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