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Acute Toxicity Study of Seed-Based Polymers in Wistar Rats: Evaluation of Safety Profile

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Abstract

Introduction: Seed-based polymers are gaining attention in pharmaceutical formulations due to their biodegradable and biocompatible nature. The present study evaluates the acute toxicity profile of three different seed-based polymers in Wistar rats. Single oral doses (2000 mg/kg) were administered as per OECD guideline 423. The study recorded mortality, body weight changes, behavioral alterations, and biochemical parameters to assess any potential toxic effects. No mortality or significant behavioral changes were observed, confirming the safety of these polymers. Histopathological examination revealed no signs of toxicity, reinforcing their biocompatibility. The findings suggest the potential safe use of these polymers in drug delivery applications and highlight the need for further studies on their long-term safety.

Material and methods: The study involved extracting, purifying, and characterizing three different seed-based polymers before use in a study. The animals were healthy female Wistar rats, housed in polypropylene cages under controlled conditions. The study adhered to OECD 423 guidelines and followed a 14-day acute toxicity study. Animals were closely monitored for signs of toxicity, mortality, and behavioural changes. Blood samples were collected at the end of the observation period, and biochemical and hematological analysis were performed. Histopathological examination of the liver, kidney, and heart tissues revealed structural alterations, inflammation, necrosis, and other histological changes indicative of toxicity. The study adhered to ethical guidelines for animal research.

Result & discussion: The study aimed to investigate the safety of seed-based polymers in treating rats with various conditions. Throughout the 14-day observation period, no mortality was reported in any of the experimental groups, and no abnormal clinical signs such as tremors, convulsions, respiratory distress, or abnormal gait were observed. The absence of these symptoms suggests that the tested seed-based polymers exhibit a high degree of safety at the administered dose.

Rats were observed for clinical signs prior to dosing, immediately after dosing, continuously for the first 30 minutes, after 4 hours, 12 hours, and daily thereafter for 14 days for morbidity and mortality. The rats were observed for changes in skin and fur, eyes, respiratory, behaviour pattern, convulsions, lethargy, sleep, and coma. Individual body weights of the rats were determined shortly before the drug administration and after 7 days and 14 days. After 14 days, the rats were euthanized with an overdose of urethane and sacrificed for gross anatomical and histopathological examinations of the liver, kidneys, and heart.

The study found that the seed-based polymers exhibited a high degree of safety at the administered dose. The effects of the seed-based polymers on body weight, lipid profile, liver function parameters, renal function markers, and hematology parameters were also examined. The results suggest that the seed-based polymers exhibit a high degree of safety at the administered dose.

Conclusion: The study concludes that the tested seed-based polymers are safe at the administered dose, supporting their potential use as pharmaceutical excipients.

Keywords: Seed-based polymers, Acute toxicity, Wistar rats, OECD 423 guideline, Drug delivery, Histopathology

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1. Introduction

Seed-based polymers have gained significant attention as potential excipients in pharmaceutical formulations due to their natural origin, biocompatibility, and biodegradability. These polymers, derived from plant seeds, offer advantages such as controlled drug release, improved stability, and compatibility with active pharmaceutical ingredients. Moreover, their sustainable and renewable nature makes them an attractive alternative to synthetic polymers in drug delivery systems. However, before incorporating these polymers into pharmaceutical formulations, a comprehensive toxicity assessment is crucial to ensure their safety and efficacy. (1-4)

Among the various seed-based polymers, those extracted from Ash Guard (Benincasa hispida), Katka (Strychnos potatorum), and Moringa (Moringa oleifera) seeds have shown promising applications in pharmaceutical and biomedical fields. These seeds contain natural coagulants and bioactive polysaccharides that possess mucoadhesive, emulsifying, and gelling properties, making them potential candidates for drug delivery systems. Ash Guard seed gum is known for its stabilizing and film-forming properties, Katka seed extract has been widely used as a water purifier due to its flocculating abilities, and Moringa seed gum exhibits antimicrobial and antioxidant properties, contributing to its pharmaceutical relevance. (5-9)

Despite their potential, the safety profile of these seed-based polymers needs thorough evaluation before their pharmaceutical application. Toxicity studies provide crucial insights into their potential adverse effects, safe dosage levels, and possible implications for human health. Acute toxicity studies, such as those conducted following the OECD 423 guideline, serve as a primary step in determining the safety of new pharmaceutical excipients. These studies assess physiological, biochemical, and histopathological parameters in animal models to establish the toxicological profile of novel excipients. (10-14)

Regulatory difference between US & Europe

The regulatory frameworks governing the safety assessment of pharmaceutical excipients, including seed-based polymers, differ notably between the United States and Europe, reflecting variations in policy approach, documentation requirements, and approval processes. In the United States, the Food and Drug Administration (FDA) oversees excipient evaluation primarily through the Inactive Ingredient Database (IID) and follows USP-NF (United States Pharmacopeia–National Formulary) standards. Excipients not listed in the IID may require additional toxicological data and potentially a Drug Master File (DMF) submission to support their use in drug formulations. The FDA typically evaluates excipients in the context of a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA), placing the burden of proof on the manufacturer to demonstrate safety within the specific formulation and dosage.

In contrast, the European Medicines Agency (EMA) manages excipient regulation under the European Pharmacopoeia and associated ICH guidelines. The Guideline on Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product requires detailed justification for the inclusion of excipients, especially novel ones. The EMA often requires a stand-alone safety evaluation of novel excipients, including full toxicological profiles, unless they are already listed in the Community Register of Excipients. Notably, Europe has a stronger emphasis on environmental impact and sustainability, aligning with its broader regulatory philosophies. Overall, while both regions prioritize safety, the EU tends to have more stringent requirements for novel excipients, often necessitating independent toxicological assessments even if the excipient has established use elsewhere. (15-19)

This study aims to evaluate the acute oral toxicity of Ash Guard, Katka, and Moringa seed-based polymers in Wistar rats. The research focuses on analyzing key physiological parameters, including body weight, food and water intake, behavioral changes, and mortality. Additionally, biochemical markers such as liver and kidney function tests, hematological parameters, and oxidative stress indicators will be examined. Histopathological analysis of major organs will further provide insights into any potential toxic effects at the cellular level. By establishing a comprehensive safety profile, this study will contribute to the potential pharmaceutical applications of these seed-based polymers, supporting their integration into drug delivery systems as safe and effective excipients. (20-26)

2. Materials and Methods

2.1. Materials

Three different seed-based polymers were extracted, purified, and characterized before use in the study. Distilled water and physiological saline were used as vehicles for polymer administration. Standard biochemical kits were procured for hematological and biochemical evaluations. The chemicals and reagents used in the study were of analytical grade and obtained from certified suppliers.

2.2. Experimental Animals

Healthy female Wistar rats (150-180 g) were selected for the study. The animals were housed in polypropylene cages under controlled environmental conditions, maintaining a temperature of 22±2°C and a 12-hour light/dark cycle. They had ad libitum access to a standard pellet diet and water throughout the study. Acclimatization was conducted for one week before dosing. The study protocol was reviewed and approved by the Institutional Animal Ethics Committee (IAEC) of Bharati Vidyapeeth College of Pharmacy, Kolhapur (BVCPK/CPCSEA/ IAEC/22/2009), and ensuring compliance with ethical guidelines for animal research.

2.3. Acute Toxicity Study

The study adhered to OECD 423 guidelines, a standardized procedure for evaluating acute oral toxicity. Three experimental groups (n=3 per polymer) received a single oral dose of 2000 mg/kg of the respective seed-based polymer, while the control group received distilled water. Post-administration, animals were closely monitored for 14 days to assess mortality, behavioral changes, signs of toxicity, and physiological responses. Observations were recorded systematically at regular intervals.

2.4. Body Weight and Behavioral Observations

Body weight measurements were taken on days 0, 7, and 14 to assess any deviations from normal growth patterns. Behavioral observations included assessments of locomotor activity, grooming behavior, respiratory distress, postural changes, and food and water intake. Any signs of distress, lethargy, tremors, or convulsions were noted to determine potential toxicological effects. (21-22)

2.5. Biochemical and Hematological Analysis

At the end of the 14-day observation period, blood samples were collected via retro-orbital puncture under light

anesthesia. Biochemical analysis included the assessment of liver function markers (ALT, AST, ALP), kidney function indicators (creatinine, blood urea nitrogen [BUN]), and total protein levels. Hematological parameters, such as red blood cell (RBC) count, white blood cell (WBC) count, hemoglobin levels, and platelet count, were evaluated to detect potential systemic toxicity. (27-28)

2.6. Histopathological Examination

Vital organs, including the liver, kidney, and heart, were carefully excised, weighed, and fixed in 10% formalin for histopathological analysis. The tissues were processed, embedded in paraffin, and sectioned for microscopic examination using hematoxylin and eosin (H&E) staining. A pathologist evaluated the slides for structural alterations, inflammation, necrosis, and other histological changes indicative of toxicity. (28-30)

3. Results and Discussion

3.1. Mortality and Clinical Signs

Throughout the 14-day observation period, no mortality was reported in any of the experimental groups. Additionally, no abnormal clinical signs such as tremors, convulsions, respiratory distress, or abnormal gait were observed. The absence of these symptoms suggests that the tested seed-based polymers exhibit a high degree of safety at the administered dose.

Rats were observed individually for clinical signs prior to dosing, immediately after dosing, continuously for first 30 min, after 4 h, 12 h and daily thereafter for 14 days for morbidity and mortality. The rats were observed for the changes in skin and fur, eyes, respiratory, behaviour pattern, convulsions, lethargy, sleep and coma. Individual body weights of the rats were determined shortly before the drug administration and after 7 days and 14 days. Body weight changes was calculated and recorded for each rat in each group. On the 14th day of treatment, all the animals were anesthetized with urethane. Blood was collected by puncturing the retro-orbital plexus with a fine glass capillary and transferred into Epindorf tubes. Serum was separated by centrifugation and utilized for the estimation of serum glucose (GOD/POD method), serum triglycerides, serum total cholesterol, serum LDL-C, HDL-C, serum albumin, serum creatinine, serum total protein, blood urea nitrogen, CRP and HbA1c using a Meril Diagnostics kit, India. After 14 days, the rats were euthanized with an overdose of urethane and sacrificed for gross anatomical and histopathological examinations of the liver, kidneys, and heart.

Table 1. Acute Oral-Toxicity study

Group	Treatment and Dose/ Day	Evaluation Parameter
I	(1 ml/kg 1% Na CMC in d.w., p.o.)	Clinical signs
NC		Skin, fur, eyes, respiratory, behaviour pattern, convulsions, lethargy, sleep and coma
II	Polymer 1 (2000 mg/kg in 1% Na CMC in d.w., p.o.)	Biochemical Parameters Serum glucose Serum Triglyceride Serum Total cholesterol
PL - I		
III	Polymer 2 (2000 mg/kg in 1% Na CMC in d.w., p.o.)	Serum LDL-C, HDL-C Serum albumin Serum creatinine Serum total protein
PL - II		
IV	Polymer 3 (2000 mg/kg in 1% Na CMC in d.w., p.o.)	Blood Urea Nitrogen
		Hematological parameter
		WBC, RBC, Platelet, Hb
		Morphological parameter Body weight, Kidney weight
PL - III		Histopathology
		Liver, kidney and heart.

*NC- Normal control, PL-I Polymer 1, PL- II Polymer 2, PL-III – Polymer 3

Table 2. Effect of Polymer 3 (Ash Guard), Polymer 2 (Katka), and Polymer 1 (Moringa)

On Body Weight		
Group	**Initial weight (g)**	**Final weight (g)**
NC	239.3 ± 10.18	241.7 ± 09.4
PL-I	231.1 ± 6.53	235.8 ± 11.4
PL-II	237.6 ± 11.25	242.8 ± 12.5
PL-III	234.2 ± 4.73	241.8 ± 10.3
On Kidney Weight		
NC	1.13 ± 0.08	1.14 ± 0.17
PL-I	1.05 ± 0.02	1.04 ± 0.09
PL-II	1.14 ± 0.04	1.08 ± 0.21

PL-III	1.11 ± 0.01	1.12 ± 0.07
On Glucose Level		
NC	105.60 ± 6.31	107.41 ± 4.07
PL-I	111.45 ± 7.36	109.21 ± 5.23
PL-II	106.14 ± 8.41	108.42 ± 5.36
PL-III	101.78 ± 9.58	103.52 ± 7.56

Data are presented as mean± SD (n=6/group). One-Way ANNOVA followed by Dunnett test

Table 3. Effect of Polymer 3 (Ash Guard), Polymer 2 (Katka), and Polymer 1 (Moringa) on lipid profile

Group	Total Cholesterol (mg/dL)	Serum Triglyceride (mg/dL)	Serum LDL-cholesterol (mg/dL)	Serum HDL-cholesterol (mg/dL)
NC	69.79 ± 7.45	79.02 ± 7.59	69.33 ± 4.7	35.47 ± 2.31
PL-I	64.45 ± 5.24	81.01 ± 7.43	61.08 ± 4.49	38.81 ± 3.72
PL-II	66.12 ± 4.67	77.01 ± 6.43	65.08 ± 6.65	40.78 ± 2.12
PL-III	69.49 ± 6.99	83.01 ± 7.25	60.08 ± 3.76	31.09 ± 4.24

Data are presented as means ± SD (n=6/group). One-Way ANNOVA followed by Dunnett test

Table 4. Effect of Polymer 3 (Ash Guard), Polymer 2 (Katka), and Polymer 1 (Moringa) on liver function parameter

Group	TP (g/dL)	T-BIL (mg/dL)	D-BIL (mg/dL)	SGPT (mg/dL)
NC	5.62 ± 0.05	0.11 ± 0.17	0.09 ± 0.02	23.27 ± 2.31
PL-I	4.45 ± 2.07	0.11 ± 0.25	0.08 ± 0.04	21.65 ± 4.45
PL-II	4.49 ± 3.78	0.10 ± 1.03	0.07 ± 0.03	29.71 ± 2.02
PL-III	5.45 ± 2.75	0.12 ± 0.42	0.09 ± 0.02	25.29 ± 3.47

Data are presented as means ± SD (n=6/group). One-Way ANNOVA followed by Dunnett test

Table 5. Effect of Polymer 3 (Ash Guard), Polymer 2 (Katka), and Polymer 1 (Moringa) on renal function markers

Group	Serum Creatinine (mg/dL)	Serum Albumin (mg/dL)	Serum BUN (mg/dL)
NC	0.29 ± 0.05	4.47 ± 0.51	20.4 ± 3.07
PL-I	0.25 ± 0.02	4.42 ± 0.21	19.47 ± 2.04
PL-II	0.26 ± 0.06	4.23 ± 0.44	21.15 ± 1.98
PL-III	0.27 ± 0.03	4.89 ± 0.26	20.44 ± 2.25

Data are presented as means ± SD (n=6/group). One-Way ANNOVA followed by Dunnett test

Table 6. Effect of Polymer 3 (Ash Guard), Polymer 2 (Katka), and Polymer 1 (Moringa) on hematology parameter

Group	RBC (×106 cells/µL)	WBC (×103 cells/µL)	Platelet (×103 cells/µL)	Haemoglobin (g/dL)
NC	7.89 ± 0.28	3.93 ± 0.42	754.0 ± 49.4	14.78 ± 0.26
PL-I	6.03 ± 0.25	3.57 ± 0.38	798.0 ± 73.7	13.59 ± 0.39
PL-II	6.98 ± 0.58	3.79 ± 0.47	747.0 ± 69.5	15.11 ± 0.26
PL-III	7.21 ± 0.54	4.07 ± 0.56	714.0 ± 47.0	14.04 ± 0.40

Data are presented as means ± SD (n=6/group). One-Way ANNOVA followed by Dunnett test

3.2. Body Weight Analysis

All treated groups maintained normal body weight throughout the study duration. No significant weight loss or growth retardation was observed in comparison to the control group. This finding suggests that the tested polymers do not interfere with metabolic functions or induce systemic toxicity that affects nutritional status.

3.3. Biochemical and Hematological Findings

Biochemical analysis revealed that all parameters, including liver and kidney function markers, remained within normal physiological limits. No significant alterations in ALT, AST, ALP, creatinine, or BUN levels were detected, indicating that the tested polymers did not induce hepatotoxicity or nephrotoxicity. Similarly, hematological parameters, such as RBC count, WBC count, hemoglobin levels, and platelet count, remained unaffected, suggesting no adverse impact on hematopoiesis or immune function.

Table 7. Heamatology & biochemistry data of test & control group

Parameters	Control	Test (200mg/kg body wt.)	Test (400mg/kg body wt.)
Hemoglobin	14.2	14.0	12.2
Haematocrit (%)	41.7	45.9	48.4
Total W.B.C.	4,960	6,894	8,750

Red blood cells	867510	845124	712560
MCV (fL)	47.9	51.24	57.61
MCHC (g/dl)	34.51	30.21	29.84
MCH(pg)	18.20	17.21	17.14
Albumin (g/dl)	2.54	2.59	2.68
AST (U/L)	81.21	76.14	68.18
ALT (U/L)	32.79	29.86	21.43
ALP (U/L)	47.51	37.35	29.31
Glucose (mg/dL)	122.83	119.71	121.39
Total Cholesterol (mg/dL)	61.87	64.29	69.46
Triglycerides(mg/dL)	32.51	30.17	28.21
HDL-C (mg/dL)	29.14	32.27	37.89
LDL-C (mg/dL)	17.19	19.12	21.19

As we observe the hematology & biochemistry of mice blood; not revealed any gross change in level of any hematological parameter, but regarding biochemical approach albumin, total cholesterol & HDL-C were found to increased slightly in test groups but it will not reach up to toxic level. Albumin is used as an indicator of liver impairment, while increase in cholesterol level in is an indicator of nutritional status, but increase in level of HDL-C good sign for because it is a Hypocholesterolemic agent. So to confirm any other further changes in body we have carried out histopathology of dissected organs.

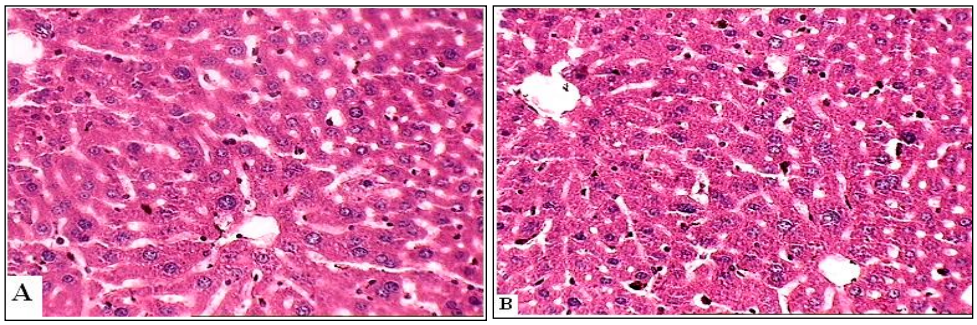

Figure 1. Histopathology of mice liver, Control group (A), Test group (B) (400mg/kg)

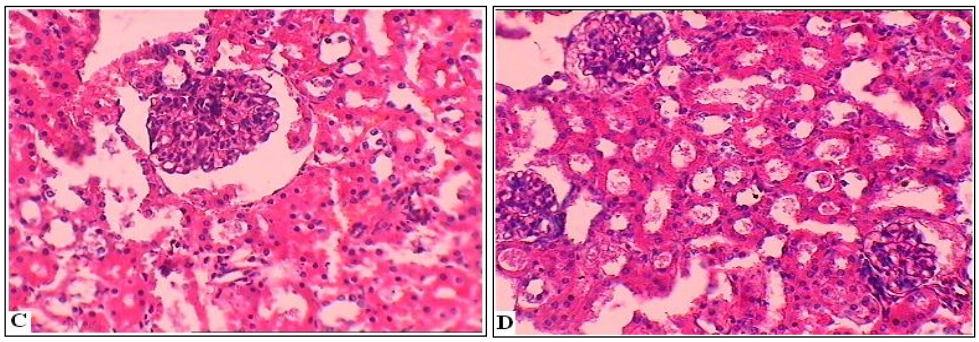

Figure 2. Histopathology of mice kidney, Control group(C), Test group (D) (400mg/kg)

No any characteristic changes were seen in the section of liver showing kuffers cells & sinusoids. Also, in kidney section no, any change has been reported in glomerular cells & tubular cells. (Paulo etal.2007)

So, from the all hematological, biochemical& histological examinations it has found that moringa coagulant is a non-toxic, harmless compound confirmed by sub-acute toxicity study. Present study was approved by IAEC committee of Bharati Vidyapeeth College of pharmacy, Kolhapur. (Approval no. BVCPK/CPCSEA/IAEC/22/2009)

3.4. Histopathological Evaluation

Microscopic examination of liver, kidney, and heart tissues showed no evidence of necrosis, cellular degeneration, inflammatory infiltration, or structural abnormalities. The histological architecture of these organs remained intact, further supporting the non-toxic nature of the tested seed-based polymers. The absence of histopathological changes reinforces the safety of these polymers for pharmaceutical applications.

An acute toxicity study was conducted to assess the safety of a single oral dose of Polymer 3 (Ash Guard), Polymer 2 (Katka), and Polymer 1 (Moringa) in rats at a dose of 2000 mg/kg body weight. The study focused on the impact of these polymers on mortality, body weight, clinical signs, internal organ morphology, and histological features, as well as on key haematology and biochemical parameters.

- General behavior: No abnormal behaviors such as lethargy, hyperactivity, or aggression were observed in the treated groups. All rats exhibited

normal activity levels, grooming behavior, and alertness.

- Physical appearance: The fur, skin, and mucous membranes of the treated rats remained normal throughout the study period. There were no signs of discoloration, rough fur, or abnormal skin texture.
- Neurological signs: No indications of neurological impairment, such as tremors, convulsions, or ataxia (uncoordinated movements), were detected in any of the treated animals.
- Respiratory patterns: Normal respiratory rates and patterns were observed, with no signs of laboured breathing, wheezing, or nasal discharge in the treatment groups.
- Food and water consumption: Rats maintained their usual levels of food and water intake throughout the study. No significant changes in appetite were observed.
- Body weight: Body weight gain in the treated groups was comparable to that of the control group, with no significant deviations indicating toxicity or poor health.
- Gastrointestinal signs: No diarrhoea, vomiting, or other gastrointestinal disturbances were noted in any of the treated animals.
- Locomotion and posture: Rats in the treated groups exhibited normal locomotion and posture. No signs of limping, dragging of limbs, or hunched posture were observed.
- Eyes: No abnormalities in eye appearance, such as redness, swelling, or discharge, were detected in any of the treated rats.

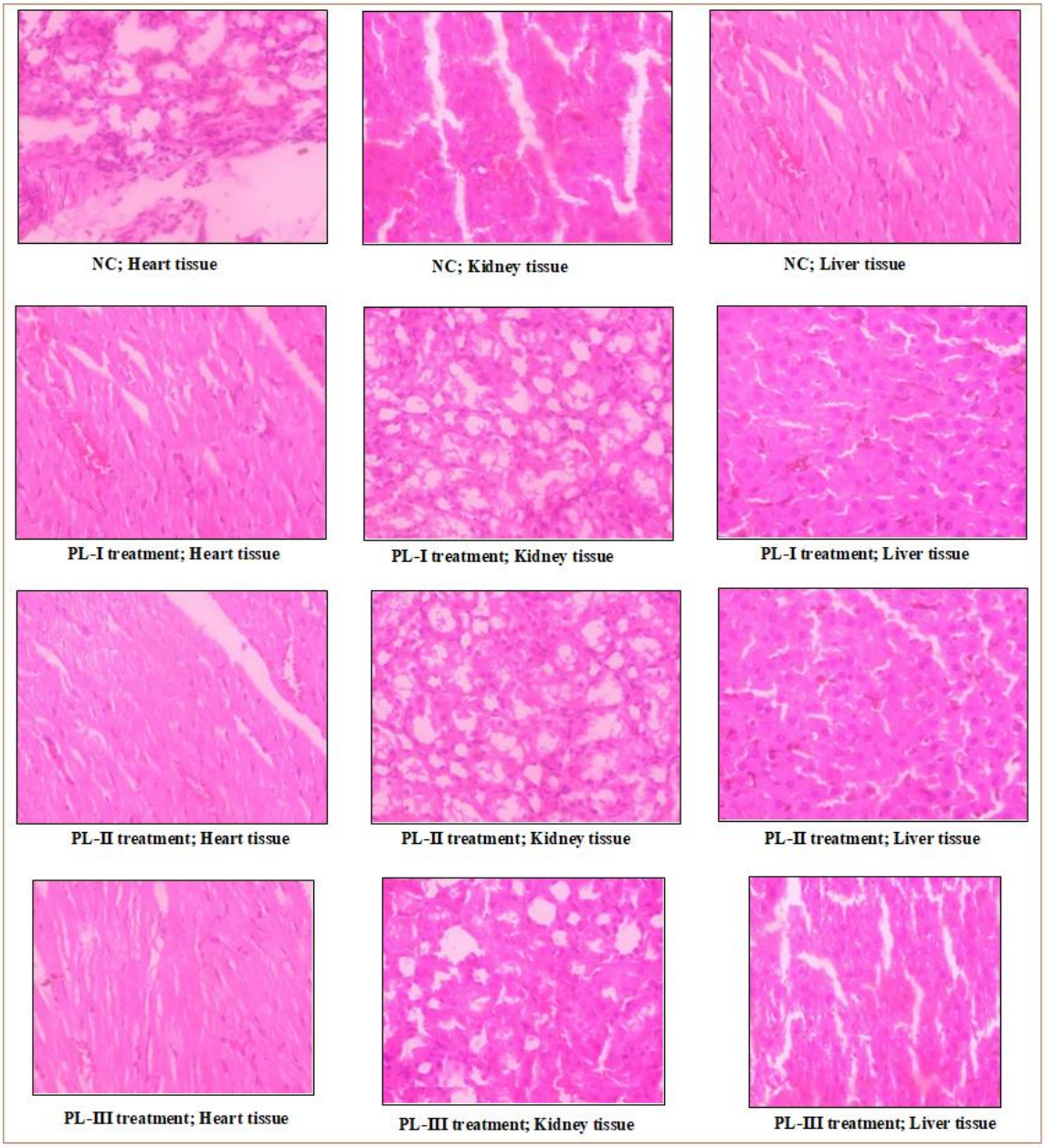

Figure 3. Histopathological Evaluation {400 X}

The administration of the polymers showed no adverse effects on the mortality rate, body weight, or general health of the animals, as evidenced by a lack of clinical symptoms. Furthermore, the morpho-histological examination of internal organs, including the heart, liver, and kidneys, revealed no abnormalities in treated rats, with normal histological features observed across all groups. In assessing the haematology and clinical biochemistry parameters, which are crucial indicators of an animal's overall health and toxicity response, the study found no significant changes between the treated groups and the controls. Liver function markers such as total protein, total bilirubin, direct bilirubin, were unaffected, indicating that the combination of these polymers did not impair liver function. Additionally, renal function markers—serum creatinine, albumin, and blood urea nitrogen (BUN)—remained within normal limits, with no significant differences observed between the combination-treated and control groups. Relative organ weights, which serve as an important safety marker in toxicity assessments, were also consistent between the treated and control groups, with no significant variations. The histopathological evaluation further supported the absence of organ-specific toxicity, showing normal tissue structures in the heart, liver, and kidneys. The results of this acute toxicity study demonstrate that the Polymer 3 (Ash Guard), Polymer 2 (Katka), and Polymer 1 (Moringa) at the given dosage are safe for oral administration in rats, as it did not result in any signs of toxicity or adverse effects on the animals' health. All treated animals displayed normal clinical health throughout the 14-day observation period. These findings provide a solid foundation for advancing to further studies to explore the therapeutic potential of these polymers.

4. Conclusion

The acute toxicity study of seed-based polymers in Wistar rats demonstrated no adverse effects at a dose of 2000 mg/kg. The findings indicate that these polymers do not induce mortality, behavioral abnormalities, biochemical imbalances, or histopathological alterations, reinforcing their safety as excipients for drug delivery systems. Based on these results, seed-based polymers hold promise for pharmaceutical applications. However, further sub-chronic and chronic toxicity studies are recommended to assess long-term safety and potential cumulative effects.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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