A Comparative Study between the Silver Based Drug Nano-Chitosan Complex and Abraxane

Dr. J. Sai Chandra[1], Mrs. A. Prasanna Lakshmi[2], Dr. K. A. Emmanuel[3], Ms. K. A. Sujitha[4], Dr. V Syamala[5], Dr. K.V.L.N. Murthy[6]

[1]Assistant Professor, Dept. of Chemistry, JNTUH University College of Engineering Sultanpur, Telangana, INDIA- 502273

[2]TGT science, A P Model school, Karempudi, Palnadu Dist., Andhra Pradesh, INDIA- 522614.

[3]Professor, Dept. of Chemistry, Y. V. N. R. Government Degree College, Kaikaluru, Eluru District. Andhra Pradesh, INDIA – 534001.

[4]II[yr] MBBS, NRI Medical College, Sanghivalasa, Visakhapatnam, Andhra Pradesh, INDIA – 531162

[5]Assistant professor. Department of chemistry. Bapatla engineering college. Bapatla, Andhra Pradesh, INDIA- 522101.

[6]Department of Chemistry, S.V.R. Degree College, Macherla, Andhra Pradesh, INDIA- 522 426.

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ABSTRACT

Biopharmaceutical research aims to develop new drug forms based on delivery systems to reduce adverse effects and prolonging the duration of the effect of the drug substance. Research on the long-term and short-term toxicological effects of the medication "Nano-chitosan complex of silver based on Schiff's base" and the medication Abraxane administered repeatedly via the stomach. Toxicity was studied with orally administration for 14 days and chronic oral toxicity for 180 days, with experimental and control groups consisting of heterosexual mice. Live weight and hematological parameters were studied. Data analysis was performed using SPSS-22. Animals demonstrated locomotor activity comparable to control and no clinical signs of any disease. The difference in scores between the groups is not significant. Hematological parameters such as bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total protein, glucose, and urea were studied. Results showed no significant differences between the groups and the Parameter of animals in the control group. Both drugs were classified as low-hazard substances. All groups of the tested animals received the researched preparations three times intragastrically, and none of these administrations had an adverse impact on the animals' vital functions, confirming the lack of subchronic toxicity. The lack of chronic toxicity of the tested medications in all groups of animals was established by many drug injections administered over the course of the 180-day investigation. The medications at the tested levels have no cumulative toxic impact that would impair the kidneys' and liver's functioning status.

Keywords: Nano-chitosan, Abraxane, subchronic, chronic, Pharmacological.

INTRODUCTION

Biopharmaceutical research focuses on developing new drugs based on delivery devices that provide targeted concentrations and reduce toxic compounds' adverse effects. Current challenges include insufficient focus, poorly studied biocompatibility, high production costs, and labor intensity. Biodegradable delivery systems are considered promising due to their low toxicity and xenobiotic effects on patients [1;2;3]. The development of biocompatible nanostructured drugs is an integral part of modern veterinary medicine [4;5]. Their obvious therapeutic benefit over counterparts in standardized dosage forms necessitates the development of regulated drug delivery approaches [6]. It has long been believed that drugs can prolong life and improve health.

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Technologies for the targeted delivery and/or controlled release of therapeutic agents are engineered into drug delivery systems [7]. Nanosized particles, advanced nanotechnology, have revolutionized carrier-mediated drug delivery, providing a potent treatment for various diseases by addressing challenges in administering low molecular weight drugs and biomacromolecules [8]. These include unfavorable physico-chemical characteristics like fluctuating solubility, poor bioavailability, and restricted stability [9]. Phospholipids, albumin, gelatin, and other biological materials have all been studied as drug delivery vehicles, as have polymers and solid metal-containing nanoparticles (NPs) [10]. NPs, due to their quick absorption by cells, have the potential to enhance drug bioavailability and uptake of poorly soluble medications through targeted delivery [11]. Biodegradable polymeric nanoparticles have gained attention as novel drug carriers due to their longer half-life, higher drug entrapment efficiency, site-specific targeting, deep penetration into skin substructures, and potential protection against harsh environmental conditions and genetic deterioration [12]. Chitosan, a biodegradable polymer with low toxicity, biocompatibility, and immunogenicity, is ideal for biomedical applications due to its low immunogenicity and antimicrobial activity [13;14]. Due to their unique properties, chitosan nanoparticles are excellent carriers for a variety of drugs, particularly hydrophobic drugs in cancer drug delivery applications, because of their small size and high surface area to volume ratio [15]. Many facets of chitosan-based nanomaterials their synthesis, properties, and use in medication delivery systems, A modification and toxicity analysis of chitosan nanoparticles [16].

Chitosan is being utilized more and more in the pharmaceutical and biomedical industries because of its non-toxicity, biocompatibility, and biodegradability [17; 18]. Chemical modifications have improved chitosan properties, particularly by forming aldehyde-functionalized chitosans. These derivatives are prepared by reacting with periodates, converting chitosan into a dialdehyde [19;20]. By reacting with nitrous acid (HNO2), aldehyde-functionalized chitosans have also been produced [21, 22]. Chitosan, containing 2, 5-anhydro-D mannose, is produced through deaminative cleavage of 1, 4-glycosidic bonds, and has been synthesized using hydrogen peroxide [23]. Dialeddehyde chitosan (DAC), which can be utilized for the development of biosensors and drug delivery applications, was produced by periodate oxidizing chitosan [24]. Tissue engineering, drug and gene delivery, wound healing, and other biomedical applications can all be readily achieved by processing chitin and chitosan into hydrogels [25;26]. Diffusion, entrapment, and tethering methods have been used to create drug-loaded chitosan hydrogels [27]. Silver's potential toxicity has been reduced and its antibacterial activity has been prolonged by chitosan membrane and its derivative [28;29].

Chitosan and its derivatives are used as stabilizing and reducing agents in an eco-friendly, simple process for producing stable Ag nanoparticles with narrow size distribution [30]. Abraxane and solvent-based paclitaxel showed LD50 values of 447 and 7.5 mg/kg in male mice and rats, respectively. A 14-day follow-up study showed decreased body weight and WBC, while 90 doses reduced weight gain and piloerection [31].

Abraxane has been studied in athymic mice, with all animals dying at 103 mg/kg, but no deaths at 30 mg/kg. The highest dose resulted in weight loss in female mice [32].

All animals in each dosage group died after 19 days due to the frank signs of toxicity caused by the Abraxane formulation, solvent-based paclitaxel, bulk paclitaxel, and Abraxane vehicle [33]. T-3761 was tested on rats, dogs, and mice, with lethal dosages of 5,000 mg/kg for rats and mice, 2,000 mg/kg for dogs, and 5,000 mg/kg for rats and mice subcutaneously. Intravenous injections led to one death in two dogs [34].

In this study, the repeated intragastric administration of Abraxane® and the "Nano-chitosan complex of silver based on Schiff's base" drug were examined for their subchronic and chronic toxicological effects.

MATERIALS AND METHODS

The vivarium at the Therapy and Pharmacology Department of the Veterinary Medicine Faculty of the RUDN University served as the foundation for the research. In order to investigate the subchronic toxicity of the resultant liposomal medication on the body, rats were employed as experimental animals. Documents pertaining to the most recent inspection of the status of the animals' health were submitted by the supplier of laboratory animals. The animals spent 14 days in a quarantine and acclimatization area. A daily examination of the animals' exterior health was done throughout this time. Animals found to be aberrant during the examination were not

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allowed to participate in the experimental groups. The animals were moved to the experimental hall of the vivarium after the quarantine period. Rats were housed in polycarbonate cages with five heads in each and steel lattice coverings over the tops. It was covered with sawdust. Ad libitum feedings of a complete extruded meal for laboratory animals were given to the animals. Psychrometric VIT-2 hygrometers were used to continuously measure the temperature and humidity in the experimental and quarantine areas of the vivarium. The microclimate's variables were manually entered. The air temperature ranged from 20 to 26 degrees Celsius, while the relative humidity ranged from 30 to 70%. mice used in experiments were divided into groups at random. In order to ensure that individual weight values did not depart from the average by more than 10%, the body weight was used as a criteria (scales V11P3. e = 0.0005 kg). (OHAUS CORPORATIN. USA, Model AX124, Mfr. No OHAUSTM 30100600/EMD). A unique number was assigned to each animal and written on its coat. The research code, breed, sex, and animal group were all written on the cells.

Males weigh (190 and 220 g) while females (196-225 g) (five females and five males) were divided into three experimental groups and one control group for the study. For 30 days, the medication was given intragastrically in dosages of 1/10 mg/kg, 1/25 mg/kg, and 1/50 mg/kg of the LD50 determined in the acute trial. Throughout the whole research time, researchers watched the animals' overall health and behavior, as well as how they responded to external stimuli like sound and light, as well as any signs of drunkenness or potential death. (DR7000D Semi-automatic chemistry analyzer, China CBC Mindray BC-3000, China).

The reference medicine Abraxane® and the drug "Nano-chitosan complex of silver based on the Schiff base" were compared in terms of their overall harmful effects.

ABRAXANE® is a registered trademark of Abraxis Bio Science, LLC. Abraxis Bio Science, LLC is a wholly owned subsidiary of Bristol-Myers Squibb Company. Company: American Pharmaceutical Partners, Inc. / American Bioscience, Inc.

ABRAXANE may cause serious side effects, including:

Severe decreased blood cell counts.

Severe nerve problems (neuropathy).

Severe infection (sepsis).

Lung or breathing problems.

Severe allergic reactions.

Subchronic toxicity

Subchronic toxicity was studied with a single intragastric administration and was observed for 14 days. This is a chronicle for 30 days (on the 10th, 20th, and 30th day of the experiment), for which experimental and control groups were formed, consisting of mice of different sexes (n = 10), selected according to the principle of pairs of analogues. Animals in the experimental groups were administered drugs in the composition of intragastric saline solution using a probe in the doses indicated in (Table1). Individuals from the control group received a dose of saline solution similar in volume.

S.No.	Group	nano-chitosan silver complex based on Schiff base, mg/kg		Abraxane® mg/kg	
		Females	**Males**	**Females**	Males
1.	(n=10) dosage 10% of LD50	750	7500	8	8,4
2.	(n=10) dosage 25% of LD50	1500	1500	20	21

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3.	(n=10) dosage 50% of LD50	3500	3500	40	42
4.	control (n=10)	Saline	Saline	Saline	Saline

Table 1. Scheme of the study of subchronic toxicity of drugs.

Chronic toxicity

Chronic oral toxicity was studied for 180 days (at 30, 60, 90, 120, 150, and 180 days of the experiment), for which experimental and control groups were also formed, consisting of heterosexual mice (n = 10), selected according to the principle of pairs-analogues. Animals in the experimental groups were administered drugs in the composition of intragastric saline solution using a probe in the doses indicated in Table 1. Individuals from the control group received a dose of saline solution similar in volume. In both trials, we studied live weight, feed and water intake, respiratory rate, behavior, and hematological parameters. To assess the toxicological properties of drugs, we were guided by the methods set forth in state standards, Federal Law No. 61 "On the Circulation of Medicines,", interstate standards, and the EAEU Leadership.

RESULTS

There were no clinical symptoms of any disease, and the animals' locomotor activity was comparable to that of controls. Between groups, there is no statistically significant difference in scores. It was investigated how hematological markers such as bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total protein, glucose, and urea affected the results. The indicators of animals in the control group did not differ significantly from the other groups, according to the results. Both medications were deemed to be low-hazardous compounds.

Subchronic toxicity

When compared to the indicators of the control group, the change is statistically significant ($p \leq 0.05$). The body weight of female did not differ significantly with dose; However, body weight of high-dose male decreased significantly ($P \geq 0.05$) with dose (Table 2).

Animal group. Dose mg / kg	**Animal weight. G**			
	Initial	**10 days**	**20 days**	**30 days**
(n=10) dosage 10% of LD50	194.8±3.73	203.6±2.1	211.3±1.8	220.2±2.1
(n=10) dosage 25% of LD50	193.2±2.21	201.9 ± 1.7	209.6±1.9	218.4±2.0
(n=10) dosage 50% of LD50	197.0±1.24	205.9±1.4	213.7±1.6	222.7±1.8
control (n=10)	195.2±2.22	204.1±1.8	211.7±2.1	220.6±1.9

Table 2. shows the dynamics of changes in the live weight of rats in the study of subchronic drug toxicity. When studying the live weight of mice, a similar dynamic was established.

Chronic toxicity

The evaluation of hematological parameters is important because toxic chemicals that harm the liver cause a rise in ALT and AST levels. The body produces more urea when there are significant levels of toxins in the primary urine. As can be observed from the statistics, there are no noticeable differences between animals in the other experimental groups and between animal indicators in they control group. Similar information was gleaned from the investigation of the medications' subchronic toxicity. As a result, the study's findings, as shown in (Table

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3;4), clearly show that the medications under examination had no negative effects on the functional state of the liver and kidneys.

Investigated hematological parameters	Unit	nano-chitosan silver complex based on the Schiff base, research days						
		Beginning of experience	30	60	90	120	150	End of experiment
The dosage of the drug is 10% of the LD50								
AST	(U/l)	55,9±1,8	56,2±2	57,8±1,9	58,0±2,5	58,7±1,5	59,3±1,3	59,5±2,3
ALT	(U/l)	60,0±2,4	62,9±2,5	63,0±2,5	63,7±2	63,4±2,8	63,2±2,6	63,2±3
Bilirubin	μmol/l	2,15±0,7	2,26±0,9	2,33±0,7	2,35±1,2	2,32±1	2,34±0,8	2,36±1
ALP	(U/l)	342±11	343±18	344±22	348±25	347±24	345±30	348±28
Urea	(mmol/l)	7,82±0,9	7,84±1,2	7,87±0,8	7,89±1,3	7,88±1,4	7,86±0,9	7,84±0,6
The dosage of the drug is 25% of the LD50								
AST	(U/l)	56,8±1,8	56,8±1,7	56,85±2	58,2±1,9	57,6±1,5	57,9±1,9	57,8±2,3
ALT	(U/l)	61,5±2,1	62,5±2,6	63,0±3	63,2±2,3	62,8±2,1	63,0±2,8	63,0±2,6
Bilirubin	μmol/l	2,36±0,6	2,35±0,9	2,31±1,2	2,38±1,0	2,30±1,3	2,37±0,9	2,33±0,8
ALP	(U/l)	351±15	348±13	350±25	358,0±26	344±13	342±26	347±27
Urea	(mmol/l)	8,0±1,0	7,74±1,2	7,80±0,5	6,2±0,5	7,81±1,5	8,02±1,2	8,21±0,7
The dosage of the drug is 50% of the LD50								
AST	(U/l)	58,4±1,7	57,94±2	57,9±1,9	57,6±1,3	57,8±1,6	57,23±1,1	58,3±2,2
ALT	(U/l)	63,3±2,2	63,04±3	63,4±2,3	63,4±2,4	63,0±2,8	65,0±2,9	65,0±2,2
Bilirubin	μmol/l	2,42±0,6	2,39±1,1	2,45±1,2	2,30±0,9	2,43±0,5	2,41±0,8	2,44±0,8
ALP	(U/l)	353±15	350±19	352±22	344±22	342±29	350±12	354±16
Urea	(mmol/l)	7,94±0,9	8,0±0,8	7,79±1,4	7,82±1,5	7,80±0,8	7,80±0,5	7,86±1,2
Control group – Saline								
AST	(U/l)	58,1±1,6	58,7±2,0	57,23±2,2	59,0±2,2	57,6±1,6	58,0±2,2	58,1±1,9
ALT	(U/l)	63,4±2,0	62,7±2,2	65,3±3,0	64,2±2,6	63,4±2,2	63,0±2,1	63,4±2,6
Bilirubin	μmol/l	2,35±1,2	2,44±1,0	2,41±0,5	2,58±0,8	2,30±1,3	2,36±1,2	2,29±0,6

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ALP	(U/l)	351±30	358±25	355±19	350±22	343±11	58,0±18	353±20
Urea	(mmol/l)	7,82±1,3	8,05±0,5	7,80±1,5	8,0±0,6	7,87±0,8	63,2±1,3	8,2±1,1

Table 3. Study of the biochemical parameters of rats after repeated intragastric administration.

Investigated hematological parameters	**Unit**	**Abraxane®, study days**						
		Beginning of experience	**30**	**60**	**90**	**120**	**150**	**End of experiment**
The dosage of the drug is 10% of LD50								
AST	(U/l)	57,3±1,5	57,6±2	58,7±1,9	59,9±1,7	60,7±1,7	62,0±1,8	62,4±1,8
ALT	(U/l)	62,2±2,9	63,2±2,5	64,0±2	64,1±2,8	65,4±3	65,9±2,2	66,3±2,4
Bilirubin	μmol/l	2,29±0,6	2,30±1,3	2,41±1,1	2,45±0,5	2,58±1	2,64±1,4	2,65±0,9
ALP	(U/l)	342±10	343±18	350±10	352±18	357±22	361±26	362±13
Urea	(mmol/l)	7,82±1,0	7,82±1,2	7,89±1,5	7,92±0,8	7,97±1,0	8,02±1,1	8,05±0,5
The dosage of the drug is 25% of LD50								
AST	(U/l)	58,6±2,2	58,0±1,9	57,8±1,9	57,6±2,1	58,8±1,5	57,6±2,1	58,1±2,0
ALT	(U/l)	63,6±2,4	63,2±2,3	63,4±2,1	63,4±3,0	63,4±2,5	63,5±2,9	63,4±2,6
Bilirubin	μmol/l	2,42±1,2	2,34±1,3	2,38±0,5	2,30±1,1	2,42±0,9	2,39±1,3	2,32±1,1
ALP	(U/l)	346±16	351±30	347±25	342±12	352,0±25	348±19	347±19
Urea	(mmol/l)	7,64±1,2	7,90±1,3	7,80±0,9	7,76±0,5	6,2±1,1	7,82±1,2	7,8±1,5
The dosage of the drug is 50% of LD50								
AST	(U/l)	57,6±2,1	57,7±1,5	56,9±1,6	57,7±2,2	58,3±1,5	58,9±2,4	58,1±2,1
ALT	(U/l)	63,4±2,6	63,1±2,7	64,4±2,5	63,2±2,1	64,4±2,9	64,6±2,1	63,4±2,4
Bilirubin	μmol/l	2,30±1,3	2,36±1,0	2,29±0,5	2,30±0,4	2,36±1,1	2,29±1,1	2,30±0,6
ALP	(U/l)	358±22	352±30	361±28	347±13	351±19	352±25	355±12
Urea	(mmol/l)	7,63±1,1	7,92±1,0	8,22±0,5	7,80±1,1	7,79±0,9	7,82±0,6	7,72±0,7
Control group - Saline solution								
AST	(U/l)	59,2±1,5	58,1±1,8	57,23±2,5	57,6±1,8	58,6±2,1	57,9±2,0	58,1±1,9
ALT	(U/l)	65,1±2,7	64,0±2,9	65,0±2,0	63,4±2,6	65,2±2,9	63,2±2,5	63,4±2,5

Bilirubin	μmol/l	2,30±0,8	2,32±1,2	2,44±1,0	2,30±1,0	2,38±0,5	2,40±0,9	2,41±0,8
ALP	(U/l)	342±15	347±10	350±23	354±20	348±13	356,0±25	347±18
Urea	(mmol/l)	7,69±1,1	7,83±0,6	7,80±0,9	7,78±1,4	7,80±0,9	63,2±0,5	7,84±0,6

Table 4. shows the results of a study of hematological parameters in rats participating in the experiment on the chronic toxicity of drugs.

Drug toxicity parameters	**nano-chitosan silver complex based on Schiff base mg/kg**		**Abraxane® mg/kg**	
	Females	**Males**	**Females**	**Males**
MTD	5000	6000	50	50
LD16	6414,5	7218,4	52,14	53,80
LD50	7520,2-7742,8	8133-8457,4	77,32-82,45	81,11-86,45
LD84	9056,2	9715,4	144,75	156,22
LD100	1230,3	1319,7	195,20	201,4
SLD50	±182,25	±174,3	±1,956	±1,795

Table 5. Indicators of acute toxicity of the studied drugs after intragastric administration.

After reviewing the study's findings, we can say that both tested medications fall under the GOST 12.1.007-76 Hazard Class 4 classification, which is the lowest level of hazard (Table 5).

DISCUSSION

Although consumer products frequently contain silver nanoparticles as bactericidal agents, little is known about how these particles might affect people. Silver is generally regarded as relatively non-toxic at doses below those that result in argyria or argyriosis [34-43]. Although it's unclear how this relates to silver nanoparticles, Wijnhoven et al.'s [35] theory states that the toxic effects of silver are directly proportional to free silver ions.

Following oral treatment, it has been demonstrated that silver absorbs through the liver via a first-pass effect, which is then excreted into the bile [36]. The renal glomerular basement membrane [37;38], the mesangium [39], the Kupffer cells, and the sinusoid endothelium cells in the liver [40;41] have all been reported to contain exposed silver.

Subchronic toxicity

The investigation's conclusions demonstrated that all groups of the animals under study did not experience any adverse effects on their vital activity after receiving three intragastric administrations of either medication. It was discovered that recurrent drug use at all tested doses did not significantly alter the clinical state of white rats when investigating subchronic toxicity in mice and rats. All of the animals in the experimental groups showed the same behavioral responses, intake of feed and water, and respiration rate, all of which were within the usual range. There were no signs of gastrointestinal or urogenital issues in the rats during the observation period. During the experiment, no animal cases of death occurred. Females and males displayed consistent weight gain dynamics as a result. The animals ate food voluntarily and put on weight over time. Throughout the experiment,

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this indicator did not change significantly. Table 2 shows that there was no reliance on the drug's dosage level. In the event that: * $p \leq 0.05$ indicates a statistically significant difference when compared to the control group's indicators [42].

Between the treated male and female and the control group, there were no appreciable variations in food or water intake. The body weight did not exhibit any significant changes in response to dose ($P<0.05$) reductions in response to dose [41;43].

Chronic toxicity

There were no abnormal behavioral responses or deaths recorded during trial feeding. Animals showed similar levels of control in their locomotor activity. Clinical indicators of any illness were also absent. The groups' scores do not significantly differ from one another.

We focused on measuring the levels of bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total protein, glucose, and urea in the study of hematological parameters in rats because liver damage from toxic substances raises ALT and AST levels. The dynamics of liver cells' toxin neutralization can be assessed using bilirubin. When there are significant levels of toxins in the primary urine, the body produces more urea in response.

The findings of an investigation into hematological parameters in rats taking part in the drug toxicity experiment over an extended period of time are displayed in Tables 3 and 4. The data acquired shows that there are no appreciable variations between them and the animal indicators in the control group [42].

ALP for mice in the middle and high-dose groups appeared to be higher, although this increase was statistically not significant, according to Kim et al. [44]. Alkaline phosphatase (ALP) levels in rats in the high-dose groups did, however, significantly increase ($P<0.01$). Both the middle- and high-dose rats and the high-dose rats had a significant increase ($P<0.01$) in cholesterol. In mice given middle-doses, there was a noteworthy rise ($P < 0.05$) in total bilirubin. According to Kim et al. [44] and Sung et al. [45], increases in alkaline phosphatase and cholesterol were also in line with liver toxicity.

Likewise, after 180 days of treatment with varying dosages of the medication, we failed to find any indication of bias in the animals' performance. Regardless of dosage, medication, or study duration, liver enzyme levels fluctuated at random. Notably, however, over the course of the experiment, the indicators of the individuals under study did not surpass the values determined for the boundaries of the reference interval.

Comparable results were found when examining the drugs' subchronic toxicity. Thus, both in the subchronic and chronic aspects, the study's findings unequivocally show that the drugs under study had no detrimental effects on the liver or kidneys' ability to function. Upon examination of the study's findings, we can conclude that both of the drugs under investigation are low-hazard substances (GOST 12.1.007–76, hazard class 4) (Table 5).

CONCLUSION

The studied preparations, when administered three times intragastrically to all groups of the studied animals, did not have a negative effect on their vital functions, which confirms the absence of subchronic toxicity. Multiple injections of drugs over the 180 days of the study confirmed the absence of chronic toxicity of the studied drugs in all groups of animals. There is no cumulative toxic effect that disrupts the functional state of the kidneys and liver from the drugs in the studied doses.

REFERENCES

1. Dreyer. F, Baur A, Biogenesis and Functions of Exosomes and Extracellular Vesicles (2016) DOI:10.1007/978-1-4939-3753-015
2. Singh. N, Joshi. A, Pal Toor. A, Verma. G, Elsevier, 865-886 (2017) https://doi.org/10.1016/B978-0-323-46143-6.00027-0

3. Ohno Shin-ichiro, Kuroda Masahiko, Exosome-Mediated Targeted Delivery of miRNAs (2016) DOI:10.1007/978-1-4939-3753-019
4. Deregibus .M.C, Figliolini. F, D'Antico. S, et. al., Int. J. Mol. Med. 38, 1359-1366 (2016)
5. Lu-Nguyen. N, Broadstock. M, Yáñez-Muñoz. R, Intrastriatal Delivery of Integration Deficient Lentiviral Vectors in a Rat Model of Parkinson's Disease (2016) 10.1007/978-1-4939-3753-0_13
6. Kastarnova, E., Orobets, V., Shahova, V., Sevostyanova, O., Belyaev, I., & Grudeva, E. (2020). Study of subchronic toxicity of the developed antibacterial drug based on exosomal particles. In E3S Web of Conferences (Vol. 175, p. 07002). EDP Sciences.
7. Shaik, M.R., M. Korsapati and D. Panati, 2012. Polymers in controlled drug delivery systems. In. J. Pharm. Sci., 2: 112-116.
8. Rodrigues, S., M. Dionísio, C.R. López and A. Grenha, 2012. Biocompatibility of Chitosan carriers with application in drug delivery. J. Functional Biomaterials, 3: 615-641. DOI: 10.3390/jfb3030615
9. Antosova, Z., M. Mackova, V. Kral and T. Macek, 2009. Therapeutic application of peptides and proteins: Parenteral forever? Trends in Biotech., 27: 628-635. DOI: 10.1016/j.tibtech.2009.07.00
10. Bamrungsap, S., Z. Zhao, T. Chen, L. Wang and C. Li et al., 2012. Nanotechnology in therapeutics. Nanomedicine, 7: 1253-1271. DOI: 10.2217/nnm.12.87
11. Suri, S.S., H. Fenniri and B. Singh, 2007. Nanotechnology-based drug delivery systems. J. Occupat. Med. Toxicol., 2: 1-6. DOI: 10.1186/1745- 6673-2-1
12. Katas, H., Z. Hussain and T.C. Ling, 2012. Chitosan nanoparticles as a percutaneous drug delivery system for hydrocortisone. J. Nanomaterials, 2012: 11-11. DOI: 10.1155/2012/372725
13. Jafarizadeh-Malmiri, H., M.A. Gaz-Jahanian and A. Berenjian, 2012. Potential applications of Chitosan nanoparticles as novel support in enzyme immobilization. Am. J. Biochem. Biotechnol., 8: 203-219. DOI: 10.3844/ajbbsp.2012.203.219
14. Vaghari, H., H. Jafarizadeh-Malmiri, A. Berenjian and N. Anarjan, 2013. Recent advances in application of Chitosan in fuel cells. Sustainable Chem. Process., 1: 16-16. DOI: 10.1186/2043-7129-1-16
15. Rajan, M. and V. Raj, 2013. Potential drug delivery applications of Chitosan based nanomaterials. Int. Rev. Chemical Eng., 5: 145-155
16. Najafi, S., Pazhouhnia, Z., Ahmadi, O., Berenjian, A., & Jafarizadeh-Malmiri, H. (2014). Chitosan nanoparticles and their applications in drug delivery: a review. Curr. Res. Drug Discov, 1, 17-25.
17. Enxian Lu, Scott Franzblan, Carmen Popesu. Preparation of aminoglycoside-loaded chitosan nanoparticles using dextran sulphate as a counter ion. J. Micro encapsulation: Micro and Nano carriers, 2009, 26(4), P. 346–354.
18. Ravi Kumar M.N.V. A review of chitin and chitosan applications. Reactive and Functional Polymers, 2000, 46, P. 1–27.
19. Vold I.M., Christensen B.E. Periodate oxidation of chitosans with different chemical Compositions. Carbohydr Res, 2005, 340, P. 679–684.
20. Xin Liu, Yunhui. Preparation process and Antimicrobial Properties of cross-linking chitosan on to periodate-oxidised bamboo pulp fabric. J. of Fibers and polymers, 2014, 15, P. 1887–1894.
21. Jolanta kumirska, Mirko X., Weinhold, Jorg Thoming, Piotr Stepnowski. Biomedical Activity of Chitin/Chitosan Based Materials- Influence of properties Apart from Molecular Weight and Degree of N-Acetylation. J. Polymer, 2011, 3, P. 1875–1901.
22. Lin C.W., Lin J.C. Characterization and blood coagulation evaluation of the water soluble chitooligosaccharides prepared by a facile fractionation method. Biomacromolecules, 2003, 4, P. 1691–1697.
23. Tian F., Liu Y., Hu K., Zhao B. Study of the depolymerization behavior of chitosan by hydrogen peroxide. Carbohydr. Polym., 2004, 57, P. 31–37.
24. Yan Feng, Limin Yang, Feng Li. A novel sensing platform based on periodate-oxidized chitosan. Anal. Methods, (2010), 2, P. 2011–2016.
25. Jayakumar R., Divya Rani V.V., Shalumon K.T., Sudheesh Kumar P.T. Nair S.V., Furuike T., et al. Bioactive and osteoblast cell attachement studies of novel α-and β-chitinmembranes for tissue engineering applications. Int. J. Biol Macromol, 2009, 45, P. 260–4.
26. Prabaharan, M., & Mano, J. F. (2004). Chitosan-based particles as controlled drug delivery systems. Drug delivery, 12(1), 41-57.
27. Lin C.C., Anseth K.S. PEG hydrogels for the controlled release of biomolecules in regenerative

medicine. Pharm. Res, 2009, 26, P. 631–43.
28. Mi F.L., Wu Y.B., Shyu S.S., Chao A.C., Lai J.Y., Su C.C. Asymmetric chitosan membranes prepared by dry/wet phase separation: a new type of wound dressing for controlled antibacterial release. J. Membr Sci, 2003, 212, P. 237–54.
29. Sharma V.K., Yangard R.A. Green Synthesis and their antimicrobial activities. J. Colloid Interface. Sci, 2009, 9, P. 83–96.
30. Preethika, R. K., Ramya, R., Ganesan, M., Nagaraj, S., & Pandian, K. (2016). Synthesis and characterization of neomycin functionalized chitosan stabilized silver nanoparticles and study its antimicrobial activity. Наносистемы: физика, химия, математика, 7(4), 759-764.
31. European Medicines Agency, Evaluation of Medicines for Human Use, ASSESSMENT REPORT FOR ABRAXANE, Procedure No. EMEA/H/C/778, UK, 2007, p – 45. https://www.ema.europa.eu/en/documents/assessment-report/abraxane-epar-public-assessment-report_en.pdf
32. Margaret E Brower, John Leighton, American Bioscience, Inc, USA, 2004, NDA No. 21, 660. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/21660_ABRAXANE_pharmr.PDF
33. Margaret E Brower, John Leighton, American Bioscience, Inc, USA, 2009, NDA No. 21, 660/ S-022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021660s022lbl.pdf
34. Nakagawa, S., Iwai, N., Komae, N., Nagasawa, M., Kawamura, Y., & Kodama, T. (1995). Single administration toxicity studies of T-3761 in mice, rats and dogs. The Japanese Journal of Antibiotics, 48(6), 754-768.
35. Wijnhoven SWP, Peijnenburg WJGM, Herberts CA, Hagens WI, Oomen AG, Heugens EHW, Roszek B, Bisschops J, Gosens I, De Meent BR, Dekkers S, De Jong, Van Jijverden MV, Sips AJAM, Geertsma RE: Nano-silver: A review of available data and knowledge gaps in human and environmental risk assessment. Nanotoxicology 2009, 3:109-138
36. Furchner JE, Richmond CR, Drake GA: Comparative metabolism of radionuclides in mammals–IV. Retention of silver-110 m in the mouse, rat, monkey, and dog. Health Phys 1968, 15:505-514
37. Creasey M, Moffat DB: The deposition of ingested silver in the rat kidney at different ages. Experientia 1973, 29:326-327.
38. Moffat DB, Creasey M: The distribution of ingested silver in the kidney of the rat and of the rabbit. Acta Anat 1972, 83:346-355.
39. Day WA, Hunt JS, McGiven AP: Silver deposition in mouse glomeruli. Pathology 1976, 8:201-204.
40. Danscher G: Light and electron microscopic localization of silver in biological tissue. Histochemistry 1981, 71:177-186.
41. Kim, Yong Soon, et al. "Subchronic oral toxicity of silver nanoparticles." Particle and fibre toxicology 7 (2010): 1-11.
42. Kastarnova, E., Orobets, V., Shahova, V., Sevostyanova, O., Belyaev, I., & Grudeva, E. (2020). Study of subchronic toxicity of the developed antibacterial drug based on exosomal particles. In E3S Web of Conferences (Vol. 175, p. 07002). EDP Sciences.
43. Roza, A., Sadoon, N., Luay Kareem, H., A Dawood, F., Muhammad Mashool, N., Rasim Karim, B., & Ahmad Alabdallah, Z. (2023). Analyzing the teratogenic potential of aluminum oxide nanoparticles (Al2O3NPs) on albino mice fetuses. Journal of Nanostructures, 13(1), 29-36.
44. Kim, Jun Sung, et al. "Antimicrobial effects of silver nanoparticles." Nanomedicine: Nanotechnology, biology and medicine 3.1 (2007): 95-101.
45. Sung JH, Ji JH, Park JD, Yoon JU, Kim DS, Jeon KS, Song MY, Jeong J, Han BS, Han JH, Chung YH, Chang HK, Lee JH, Cho MH, Kelman BJ, Yu IJ: Subchronic inhalation toxicity of silver nanoparticles. Toxicol Sci 2009, 108(2):452-61.