Pharmacophore

ISSN-2229-5402

Journal home page: http://www.pharmacophorejournal.com

EFFECT OF SILVER NANOPARICLES ON NONSPECIFIC PROTEOLYSIS IN THE GASTRIC MUCOSA AT ULCERATIVE DAMAGE MODELING

Magomed Khasainovich Gairabekov[1], Tamerlan Borisovich Vakalishev[2], Isa Fahriddinovich Khurshidov[3], Alyona Sergeevna Vasilyeva[3], Gunel Ilgar Kyzy Imamedova[1], Rovda Pahrudievna Khidrazova[4], Tatyana Sergeevna Gambaryan[1], Aslan Ruslanovich Kazimagomedov[5*]

1. ***Department of Therapy, Faculty of Pediatrics, Rostov State Medical University, Rostov-on-Don, Russia.***
2. ***Department of Therapy, Faculty of Medicine, Ingush State University, Magas, Russia.***
3. ***Department of Therapy, Faculty of Medicine, Astrakhan State Medical University, Astrakhan, Russia.***
4. ***Department of Therapy, Faculty of Medicine, North-Ossetian State Medical Academy, Vladikavkaz, Russia.***
5. ***Department of Therapy, Faculty of Medicine, Stavropol State Medical University, Stavropol, Russia***

ARTICLE INFO

Received:
10 March 2024
Received in revised form:
29 May 2024
Accepted:
03 June 2024
Available online:
28 June 2024

Keywords: Gastric ulcer, Nanosilver, Proteinases, Proteinase inhibitors, Inflammation

ABSTRACT

The effect of silver nanoparticles (Ag NPs) at oral administration on the gastric mucosa of intact animals and possible prevention of acute gastric ulcer formation has been studied. The indices of nonspecific proteinases and their inhibitors in blood serum and the supernatant of gastric mucosal homogenate were evaluated. It has been established that the use of Ag NPs solution as a drinking substrate in intact animals is accompanied by a minimal reaction of the components of proteinase inhibitory systems both at the systemic and local levels. Prophylactic use of Ag NPs solution in modeling acute gastric ulcers leads to inhibition of activation of nonspecific proteinases and preservation of inhibitory potential, which may indicate the presence of anti-inflammatory effects of Ag NPs. The inhibition of the activation of proteolytic enzymes and the preservation of a sufficiently high inhibitory potential of the Ag NPs solution as a preventive means for the formation of an ulcerative defect of the gastric mucosa indicates the presence of anti-inflammatory effects of Ag NPs, which is the basis for further research.

To Cite This Article: Gairabekov MKh, Vakalishev TB, Khurshidov IF, Vasilyeva AS, Imamedova GIK, Mamaeva MB, et al. Effect of Silver Nanoparticles on Nonspecific Proteolysis in the Gastric Mucosa at Ulcerative Damage Modeling. Pharmacophore. 2024;15(3):27-33. https://doi.org/10.51847/TDwjSvAV6Q

Introduction

Currently, more and more attention of researchers is focused on exploring the possibilities of using nanotechnology to modify and develop medicines [1, 2]. Special attention in this direction is attracted by the use of metal nanoparticles (Me NPs), the biological activity of which increases significantly in the nanoscale range [3, 4].

Modification of silver using nanotechnology makes it possible to reduce the concentration of the metal hundreds of times while maintaining all its bactericidal properties [5, 6]. There are indications in the literature of the high antimicrobial activity of silver nanoparticles (Ag NPs) against a wide range of Gram-positive and Gram-negative bacteria [7, 8]. However, insufficient attention is paid to the study of the anti-inflammatory effects of Ag NPs, apparently associated with its antibacterial effect [9, 10]. At the same time, the possibilities of using Ag NPs require further detailed study due to the insufficiently studied toxicological effect of the drug on the body [11-13].

Corresponding Author: Ruslanovich Kazimagomedov; Department of Therapy, Faculty of Medicine, Stavropol State Medical University, Stavropol, Russia. E-mail: bucky99@yandex.ru.

One of the experimental models that can be used to study the effects of Ag NPs is the model of ulcerative damage to the mucous membrane of the gastroduodenal zone of the gastrointestinal tract, which can be considered from the point of view of a typical inflammatory process [14, 15]. Moreover, when modeling acute gastric ulcers, activation of the components of the proteinase-inhibitory system plays an essential role and their study can be effectively used to study a variety of factors affecting the formation of inflammation [11-17].

Thus, the study aimed to study the effects of Ag NPs in oral administration on the gastric mucosa of intact rats and in modeling acute gastric ulcers based on an assessment of systemic and local reactions of nonspecific proteinases and their inhibitors.

Materials and Methods

An experimental study was carried out on 38 white male rats weighing 180-210 g. The study was approved by the Bioethics Committee of the University in compliance with the principles of the European Convention for the Protection of Vertebrates Used for Experimental and Other Purposes [18]. Two series of experiments were conducted. In the first series, the effect of Ag NPs on the tissues of the gastric mucosa of rats was studied by oral administration without modeling pathology. For this purpose, laboratory animals of the experimental group (n = 9) were watered with a solution of Ag NPs with a concentration of 0.01 g/L for 21 days. As a control group (n = 9), animals that were on a free drinking regime with distilled water were used. At the end of the specified period, the animals were removed from the experiment under ether anesthesia, followed by the collection of material for research. In the second series of experiments, the preventive effect of Ag NPs solution on the formation of experimental ulcerative damage to the gastric mucosa was studied. For this purpose, an Ag NPs solution was used as a drinking substrate in a group of laboratory animals (n = 10) for 21 days. At the end of the specified period, gastric ulcers were simulated by subcutaneous administration of indomethacin to animals at a dosage of 35 mg/kg body weight after 24 hours of fasting. As a control, a group of animals (n = 10) received distilled water for drinking. Euthanasia of animals was carried out 24 hours after modeling ulcerative damage under ether anesthesia by decapitation followed by material collection. Ag NPs solution was synthesized by the method of chemical reduction [19]. The composition of the test solution includes Ag NPs with a size of 10-20 nm (0.1%), sodium alginate (0.6%), and distilled water (99.3%). Before the start of the experimental study, the initial solution was diluted with distilled water in a ratio of 1:99.

The material for the research was blood serum and a supernatant of gastric mucosal homogenate, which was obtained according to the method described by Badran *et al*. [20]. The activity of the components of the proteinase inhibitory system was determined using enzymatic methods [21] on an SF-2 spectrophotometer (Spectophysics, Russia). The method for determining trypsin-like activity is based on spectrophotometric measurement of the rate of cleavage of N-benzoyl-L-arginine from the synthetic substrate of N-benzoyl-Larginine ethyl ether. The elastase-like activity was determined based on the study of the hydrolysis rate of the synthetic substrate N-tBOC-alanyl-p-nitrophinyl ether. The concentration of alpha-1 proteinase inhibitor was determined based on inhibition of cleavage by trypsin. Similarly, the activity of acid-stable inhibitors was determined after the preliminary preparation of serum by heating in an acidic environment [22]. The protein in all samples was determined by the Lowry method [23].

To assess the pathomorphological changes in the gastric tissues, serial sections with a thickness of 4-5 microns were prepared, which were stained with hematoxylin-eosin. Viewing and digital photographs of micro-preparations were carried out using an Olympus CX-41 light microscope (Olympus, USA).

Statistical processing of the obtained data was carried out using methods of variational statistics with calculation of averages (M), estimation of the probability of discrepancies (m), and assessment of the reliability of changes using the Student's t-test. The difference of the average values at $p < 0.05$ was taken as reliable.

Results and Discussion

The results of the studies conducted in the first series of experiments showed that prolonged oral administration of Ag NPs solution did not lead to significant changes in the state of the components of the proteinase inhibitory system both in blood serum and at the local level. As can be seen from the presented results **(Table 1)**, in blood serum, the study of nonspecific proteinases and their inhibitors revealed no differences in the groups treated with Ag NPs solution and distilled water. A similar situation was noted at the local level. In the supernatant of gastric mucosal homogenate, the use of Ag NPs solution as a drink was characterized by mild changes in elastase-like activity (ELA) and trypsin-like activity (TLA), as well as acid-stable inhibitors (ASI). However, of all the studied indicators, attention is drawn to a decrease in the level of antitryptic activity (ATA) by 70% compared with its level in the control group **(Table 2)**. Nevertheless, the absence of an increase in the activity of both trypsin-like and elastase-like proteinases indicates the preservation of a sufficient level of antiproteinase potential in the gastric mucosa.

Table 1. Changes in the parameters of proteinases and their inhibitors in the blood serum of rats without modeling pathology with oral administration of Ag NPs solution

Index	Control	Ag NPs
	***n*=9**	***n*=9**

ELA, µM/mg×min	M±m	1,57±0,48	1,66±0,25
	p_1		>0,5
TLA, µM/mg×min	M±m	0,49±0,08	0,40±0,06
	p_1		>0,5
ATA IE/mg	M±m	34,81±6,02	41,41±5,01
	p_1		>0,5
ASI, IE/mg	M±m	7,07±0,82	5,58±0,52
	p_1		>0,25

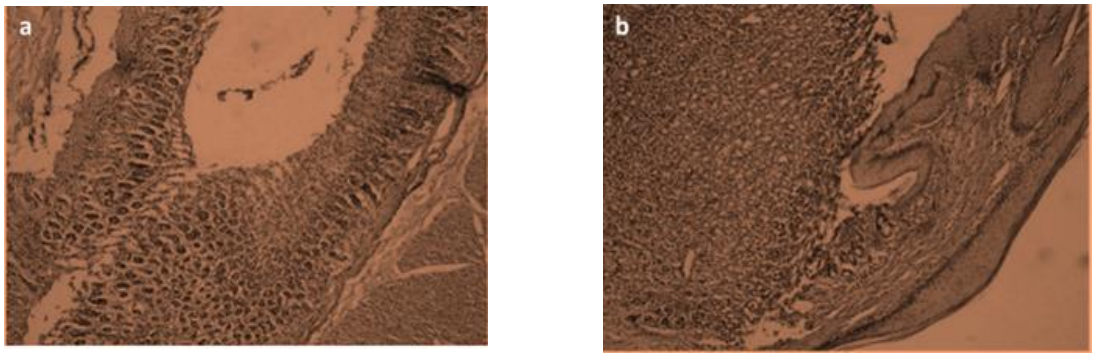
Where: ELA is elastase-like activity, TLA is trypsin-like activity, (ATA) is antitryptic activity, ASI is acid-stable inhibitors, p is – statistically significant correlations.

Table 2. Changes in the parameters of proteinases and their inhibitors in the supernatant of the homogenate of the gastric mucosa of rats without modeling pathology with oral administration of Ag NPs solution

Index		**Control**	**Ag NPs**
		***n*=9**	***n*=9**
ELA, µM/mg×min	M±m	29,60±3,47	36,76±7,86
	p_1		>0,5
TLA, µM/mg×min	M±m	29,09±3,32	21,94±4,15
	p_1		>0,5
ATA IE/mg	M±m	78,74±4,14	23,47±1,70
	p_1		<0,01
ASI, IE/mg	M±m	21,01±2,66	24,20±1,78
	p_1		>0,5

Where: ELA is elastase-like activity, TLA is trypsin-like activity, (ATA) is antitryptic activity, ASI is acid-stable inhibitors, p is – statistically significant correlations.

Microscopic examination of the stomachs of rats of both the control and experimental groups revealed a similar histological pattern inherent in individuals of this age. The gastric mucosa of the control group rats was characterized by numerous folds covered with a single-layer prismatic epithelium. Numerous glands containing main, parietal and mucous exocrinocytes were located in the own plate of the mucosa, various immunocompetent cells were found diffusely located in the stroma, and single lymphoid follicles were found in the submucosal layer **(Figure 1a)**. During histological examination of the gastric mucosa of rats, which were watered with Ag NPs solution, the picture was similar to the above, but the main feature was a more pronounced ability of the mucosa to follicle formation. Thus, in several sections, against the background of an intact mucosa, a slightly increased number of lymphoid follicles in the submucosal layer is determined, which may indicate the activation of local immune defense factors **(Figure 1b)**.



a) b)

Figure 1. Histological examination of samples: histological structure of the stomach wall of a rat in the control group at ×400 magnification (a), mucous membrane of the esophageal-gastric junction of a rat with oral administration of an Ag NPs solution at ×100 magnification (b).

In the second series of experiments, more significant shifts in the proteinase inhibitory system were noted when modeling gastric ulcers. Thus, in blood serum 24 hours after ulcer modeling, there was a tendency to increase elastase-like and trypsin-like proteases against the background of increased antitryptic activity **(Table 3)**. At the local level, more pronounced shifts in the components of the proteinase inhibitory system were observed in the gastric mucosa, as evidenced by a significant increase in elastase-like activity by 160% and trypsin-like activity by 45% compared to the control. Moreover, against the background

of an increase in the activity of proteinases, there was a significant decrease in the level of antitryptic activity and acid-stable inhibitors by 40% and 33%, respectively.

Table 3. Changes in the parameters of proteinases and their inhibitors in blood serum during the simulation of gastric ulcer against the background of oral administration of Ag NPs solution

Index		Control	Stomach ulcer	Stomach ulcer + Ag NPs
		***n*=9**	***n*=10**	***n*=10**
ELA, μM/mg×min	M±m	1,57±0,48	2,06±0,26	1,85±0,24
	p_1		>0,5	>0,5
	p_2			>0,5
TLA, μM/mg×min	M±m	0,49±0,08	0,50±0,15	0,28±0,09
	p_1		>0,5	>0,1
	p_2			>0,25
ATA IE/mg	M±m	34,81±6,02	37,44±3,34	29,57±3,83
	p_1		>0,5	>0,5
	p_2			>0,5
ASI, IE/mg	M±m	7,07±0,82	6,75±1,08	6,91±0,62
	p_1		>0,5	>0,5
	p_2			>0,5

Where: ELA is elastase-like activity, TLA is trypsin-like activity, (ATA) is antitryptic activity, ASI is acid-stable inhibitors, p is – statistically significant correlations.

The preventive use of Ag NPs solution as a drinking substrate for 21 days before modeling ulcerative damage to the gastric mucosa led to less pronounced shifts in the parameters of the components of the proteinase inhibitory system. Moreover, if at the systemic level, there was only a tendency to decrease the level of non-specific proteases **(Table 3)**, then at the local level in the gastric mucosa there was a significantly less pronounced activation of proteolytic enzymes with simultaneous stabilization of the inhibitory potential. Thus, the activation level of elastase-like and trypsin-like activities was 30% and 37% lower, respectively, than the average values in the group with gastric ulcer modeling, while the TPA value remained at the control level. Proteinase inhibitors, on the contrary, remained at a relatively high level, as evidenced by higher antitryptic activity, 38% higher than in the group without the use of Ag NPs, and the level of acid-stable inhibitors, which was also 21% higher **(Figure 2)**.

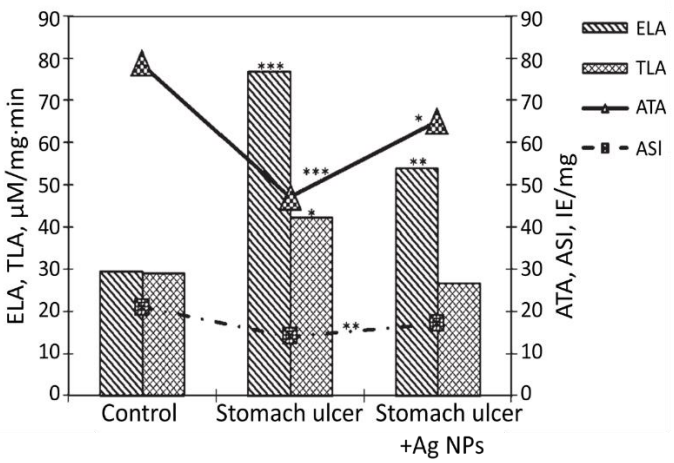
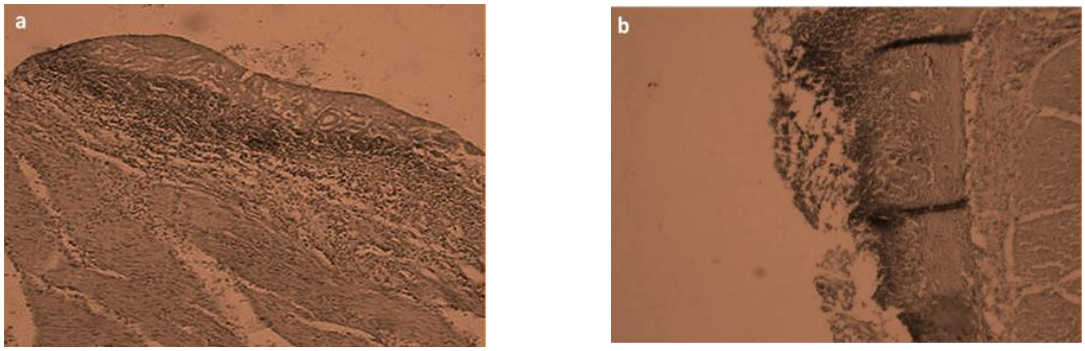


Figure 2. Changes in the parameters of proteinases and their inhibitors in the supernatant of gastric mucosal homogenate in the simulation of gastric ulcer against the background of oral administration of Ag NPs solution. The reliability of the differences in relation to the control was set at p<0.001. ELA is elastase-like activity, TLA is trypsin-like activity, (ATA) is antitryptic activity, and ASI is an acid-stable inhibitor.

The revealed changes in the proteolysis system in the modeling of acute gastric ulcers were accompanied by characteristic morphological changes in the mucous membrane, which were characterized by significant inflammatory and destructive changes. Thus, pronounced edema, massive neutrophil infiltration, and vascular fullness were detected throughout the entire volume of the section. The bottom of the ulcerative defect was a muscle layer covered with leukocyte tissue detritus and fibrinous exudate **(Figure 3a)**. The morphological picture of the gastric mucosa of rats in the group with oral prophylactic use

of Ag NPs solution for gastric ulcer was also characterized by the presence of an ulcer defect, inflammatory hyperemia, and edema, however, the depth of the ulcer and the severity of leukocyte infiltration were significantly less **(Figure 3b)**.



a) b)

Figure 3. Histological examination of samples: the bottom of a rat gastric ulcer without the use of Ag NPs solution at ×100 magnification. Rat gastric mucosa in the simulation of acute ulcers on the background of oral administration of Ag NPs solution at ×100 magnification.

Thus, as studies have shown, the use of Ag NPs solution as a drinking substrate for intact animals for a long time did not lead to significant changes in the proteinase inhibitory system both at the systemic and local levels, which indicates the absence of proinflammatory effects in the studied solution [24].

The preventive use of Ag NPs solution as a prevention of the formation of gastric ulcers led to the development of less pronounced manifestations of ulcerative damage to the gastric mucosa than in the group of laboratory animals that drank only distilled water. In our experiment, it was shown that the modeling of acute gastric ulcer, in addition to morphological changes, is accompanied by an acute phase reaction of the components of the proteolysis system, more pronounced at the local level, as evidenced by a significant increase in elastase and trypsin-like activity with a simultaneous decrease in antitryptic activity and the level of acid-stable inhibitors. Oral use of Ag NPs before modeling gastric ulcer, on the contrary, leads to the development of less pronounced manifestations of ulcerative damage to the gastric mucosa. Thus, when studying the activities of proteinases and their inhibitors, it was found that at the local level, prophylactic oral administration of Ag NPs solution for 21 days preceding the modeling of acute gastric ulcer is characterized by a weaker activation of nonspecific proteases by the end of the first day after the model was performed, and the inhibitory potential remains at a fairly high level. In addition, when using Ag NPs, there are less pronounced manifestations of signs of inflammatory alteration at the morphological level.

Obviously, the possible effects of sodium alginate, which is part of the test solution, should be also taken into account. Thus, preparations with sodium alginate have found wide application in practical medicine as an ambulance for heartburn and treatment of gastroesophageal reflux disease [25-27]. However, an analysis of the literature has shown that the mechanism of action of sodium alginate is primarily aimed at eliminating acid aggression by forming a so-called gel that protects the mucous membrane of the esophagus and is also associated with the formation of a mechanical barrier-a raft that prevents the stomach contents from being thrown into the esophagus [28-30]. It is worth noting, that sodium alginate does not completely prevent the development of destructive damage and impaired gastric tropism, but only reduces the risk of developing a deep pathology [31].

Anyway, the use of Ag NPs in combination with sodium alginate contributes to the formation of less pronounced manifestations of ulcerative defect in the modeling of acute gastric ulcers, which justifies the possibility of its use for the prevention of the development of gastroduodenal ulcers.

Conclusion

Thus, oral administration of Ag NPs solution as a drinking substrate for a long period in intact animals is accompanied by a weakly expressed reaction of the components of the proteinase inhibitory system both at the systemic and local levels, which indicates the minimal effects of Ag NPs on the reaction of intact tissues of the gastric mucosa. Preventive oral use of Ag NPs leads to the development of less pronounced manifestations of ulcerative mucosal damage in the modeling of gastric ulcers, as evidenced by a lower level of activation of nonspecific proteinases while maintaining a high inhibitory potential than in the group without the use of Ag NPs. The inhibition of the activation of proteolytic enzymes and the preservation of a sufficiently high inhibitory potential of the Ag NPs solution as a preventive means for the formation of an ulcerative defect of the gastric mucosa indicates the presence of anti-inflammatory effects of Ag NPs, which is the basis for further research.

Acknowledgments: All the authors were involved in the conceptualization, methodology, formal analysis, writing, and editing of the manuscript.

Conflict of interest: None

Financial support: None

Ethics statement: Teeth samples were obtained from patients after signing a volunteer agreement for the use of their biomaterial in the experiment. All raw data are available upon request from the corresponding author.

References

1. Doroudian M, O'Neill A, Mac Loughlin R, Prina-Mello A, Volkov Y, Donnelly SC. Nanotechnology in pulmonary medicine. Curr Opin Pharmacol. 2021;56:85-92. doi:10.1016/j.coph.2020.11.002
2. Sindhwani S, Chan WCW. Nanotechnology for modern medicine: Next step towards clinical translation. J Intern Med. 2021;290(3):486-98. doi:10.1111/joim.13254
3. Sawah D, Sahloul M, Ciftci F. Nano-material utilization in stem cells for regenerative medicine. Biomed Tech (Berl). 2022;67(6):429-42. doi:10.1515/bmt-2022-0123
4. Alzate-Correa D, Lawrence WR, Salazar-Puerta A, Higuita-Castro N, Gallego-Perez D. Nanotechnology-driven cell-based therapies in regenerative medicine. AAPS J. 2022;24(2):43. doi:10.1208/s12248-022-00692-3
5. Bruna T, Maldonado-Bravo F, Jara P, Caro N. Silver nanoparticles and their antibacterial applications. Int J Mol Sci. 2021;22(13):7202. doi:10.3390/ijms22137202
6. Xu L, Wang YY, Huang J, Chen CY, Wang ZX, Xie H. Silver nanoparticles: Synthesis, medical applications and biosafety. Theranostics. 2020;10(20):8996-9031. doi:10.7150/thno.45413
7. Yin IX, Zhang J, Zhao IS, Mei ML, Li Q, Chu CH. The antibacterial mechanism of silver nanoparticles and its application in dentistry. Int J Nanomedicine. 2020;15:2555-62. doi:10.2147/IJN.S246764
8. Swolana D, Wojtyczka RD. Activity of silver nanoparticles against staphylococcus spp. Int J Mol Sci. 2022;23(8):4298. doi:10.3390/ijms23084298
9. Almatroudi A. Silver nanoparticles: Synthesis, characterization and biomedical applications. Open Life Sci. 2020;15(1):819-39. doi:10.1515/biol-2020-0094
10. Blinov AV, Nagdalian AA, Povetkin SN, Gvozdenko AA, Verevkina MN, Rzhepakovsky IV, et al. Surface-oxidized polymer-stabilized silver nanoparticles as a covering component of suture materials. Micromachines (Basel). 2022;13(7):1105. doi:10.3390/mi13071105
11. Tăbăran AF, Matea CT, Mocan T, Tăbăran A, Mihaiu M, Iancu C, et al. Silver nanoparticles for the therapy of tuberculosis. Int J Nanomedicine. 2020;15:2231-58. doi:10.2147/IJN.S241183
12. Sakthi Devi R, Girigoswami A, Siddharth M, Girigoswami K. Applications of gold and silver nanoparticles in theranostics. Appl Biochem Biotechnol. 2022;194(9):4187-219. doi:10.1007/s12010-022-03963-z
13. Kaukab A, Gaur S, Agnihotri R, Taneja V. Silver nanoparticles as an intracanal medicament: A scoping review. ScientificWorldJournal. 2023;2023:9451685. doi:10.1155/2023/9451685
14. Medina-Reyes EI, Rodríguez-Ibarra C, Déciga-Alcaraz A, Díaz-Urbina D, Chirino YI, Pedraza-Chaverri J. Food additives containing nanoparticles induce gastrotoxicity, hepatotoxicity and alterations in animal behavior: The unknown role of oxidative stress. Food Chem Toxicol. 2020;146:111814. doi:10.1016/j.fct.2020.111814
15. Mahmood Z, Mousa E, Adday S. Preparation and characterization of Nano silver nitrate by Pyrus communis plant extract (peel and seeds) and biological activity study. J Med Pharm Chem Res. 2022;4(8):732-40.
16. Mehraliyeva S, Valiyeva M, Abbasli N, Suleymanova T, Musayeva S, Davaran S, et al. Development of novel antibacterial gel using clove and calendula extracts with colloidal silver nanoparticles. J Med Pharm Chem Res. 2021;3(3):170-9.
17. Sousa A, Bradshaw TD, Ribeiro D, Fernandes E, Freitas M. Pro-inflammatory effects of silver nanoparticles in the intestine. Arch Toxicol. 2022;96(6):1551-71. doi:10.1007/s00204-022-03270-w
18. Petetta F, Ciccocioppo R. Public perception of laboratory animal testing: Historical, philosophical, and ethical view. Addict Biol. 2021;26(6):e12991. doi:10.1111/adb.12991
19. Kravtsov AA, Blinov AV, Nagdalian AA, Gvozdenko AA, Golik AB, Pirogov MA, et al. Acid-base and photocatalytic properties of the CeO_2-Ag nanocomposites. Micromachines (Basel). 2023;14(3):694. doi:10.3390/mi14030694
20. Badran D, El-Agroudy AE, Kassab AA, El-Bayoumi KS, Eldken ZH, Elswaidy NRM. Impact of peripheral blood mononuclear cells preconditioned by activated platelet supernatant in managing gastric mucosal damage induced by zinc oxide nanoparticles in rats. Anat Cell Biol. 2024;57(1):105-18. doi:10.5115/acb.23.217
21. Soleimany AP, Martin-Alonso C, Anahtar M, Wang CS, Bhatia SN. Protease activity analysis: A toolkit for analyzing enzyme activity data. ACS Omega. 2022;7(28):24292-301. doi:10.1021/acsomega.2c01559
22. Zhou Y, Dun Y, Fu H, Wang L, Pan X, Yang X, et al. Design, synthesis, and preliminary bioactivity evaluation of N-benzylpyrimidin-2-amine derivatives as novel histone deacetylase inhibitor. Chem Biol Drug Des. 2017;90(5):936-42. doi:10.1111/cbdd.13019
23. Waterborg JH, Matthews HR. The Lowry method for protein quantitation. Methods Mol Biol. 1984;1:1-3. doi:10.1385/0-89603-062-8:1
24. Choudhary A, Singh S, Ravichandiran V. Toxicity, preparation methods and applications of silver nanoparticles: An update. Toxicol Mech Methods. 2022;32(9):650-61. doi:10.1080/15376516.2022.2064257

25. Kong X, Chen L, Li B, Quan C, Wu J. Applications of oxidized alginate in regenerative medicine. J Mater Chem B. 2021;9(12):2785-801. doi:10.1039/d0tb02691c
26. Li S, Zhang H, Chen K, Jin M, Vu SH, Jung S, et al. Application of chitosan/alginate nanoparticle in oral drug delivery systems: prospects and challenges. Drug Deliv. 2022;29(1):1142-9. doi:10.1080/10717544.2022.2058646
27. Farshidfar N, Iravani S, Varma RS. Alginate-based biomaterials in tissue engineering and regenerative medicine. Mar Drugs. 2023;21(3):189. doi:10.3390/md21030189
28. Gomez Cifuentes JD, Sparkman J, Graham DY. Management of upper gastrointestinal symptoms in patients with autoimmune gastritis. Curr Opin Gastroenterol. 2022;38(6):600-6. doi:10.1097/MOG.0000000000000878
29. Iglesias N, Galbis E, Romero-Azogil L, Benito E, Lucas R, García-Martín MG, et al. In-depth study into polymeric materials in low-density gastroretentive formulations. Pharmaceutics. 2020;12(7):636. doi:10.3390/pharmaceutics12070636
30. Shakya S, Tiwari RK, Gupta A. Gum-based nanoparticles targeting for colon rectal cancer: Latest research and patents. Recent Adv Drug Deliv Formul. 2023;17(4):255-63. doi:10.2174/0126673878242191231017095804
31. Islam MM, Raikwar S. Enhancement of oral bioavailability of protein and peptide by polysaccharide-based nanoparticles. Protein Pept Lett. 2024;31(3):209-28. doi:10.2174/0109298665292469240228064739