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EFFECT OF CHITOSAN ON THE ACTIVITY OF ANTIMICROBIAL AGENTS *IN VITRO*

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The effect of chitosan on the efficacy of antimicrobial drugs was studied *in vitro*. It was established that the enterosorbents Lactofiltrum®, Chitosan Evalar®, and Enterosgel® exert no significant impact on the activity of antibiotics such as ciprofloxacin, amoxiclav, clarithromycin, and cefoperazone. Low-molecular-weight crab chitosan (molecular weight (MW): 50 kDa; degree of deacetylation (DD): 85.0%) was found to enhance the efficacy of aminoglycosides (gentamicin and kanamycin), macrolides (clarithromycin), and fluoroquinolones (lomefloxacin and ofloxacin). Medium-molecular-weight crab chitosan (MW: 83.7 kDa; DD: 89.0%) showed a reduction in ofloxacin and lomefloxacin activity by 26.7% and 24.1%, respectively. High-molecular-weight fungal chitosan derived from *Rhizopus oryzae* F-814 (MW: 400 kDa; DD: 86.8%; ATCC 9363, NRRL 395, IMI 40564) exhibited a 25.4%–57.1% increase in ofloxacin efficacy, highlighting its potential for pharmacological applications. Preliminary sorption of antibiotics onto chitosan for two hours enhanced the antimicrobial effects observed under sequential administration of antibiotic solutions into assay wells.

Keywords: chitosan, enterosorbent, antibacterial activity, antibiotic, *Rhizopus oryzae*
Conflict of interest: the authors declare no conflict of interest.
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ВЛИЯНИЕ ХИТОЗАНА НА АКТИВНОСТЬ АНТИМИКРОБНЫХ ПРЕПАРАТОВ *IN VITRO*

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Проведено исследование влияния хитозана на эффективность антимикробных препаратов в условиях *in vitro*. Установлено, что энтеросорбенты «Лактофильтрум»®, «Хитозан Эвалар»® и «Энтеросгель»® не оказывают значимого влияния на активность антибиотиков, таких как ципрофлоксацин, амоксиклав, кларитромицин и цефоперазон. Низкомолекулярный крабовый хитозан (молекулярная масса (ММ): 50 кДа; степень деацетилирования (СД): 85,0%) повысил эффективность аминогликозидов (гентамицина и канамицина), макролидов (кларитромицина) и фтохинолонов (ломефлоксацина и офлоксацина). Среднемолекулярный крабовый хитозан (ММ: 83,7 кДа; СД: 89,0%) показал снижение активности офлоксацина и ломефлоксацина на 26,7 и 24,1% соответственно. Высокомолекулярный грибной хитозан из *Rhizopus oryzae* F-814 (ММ: 400 кДа;

СД: 86,8%; ATCC 9363, NRRL 395, IMI 40564) продемонстрировал увеличение эффективности офлоксацина на 25,4–57,1%, что делает его перспективным для фармакологического применения. Предварительная сорбция антибиотиков на хитозане в течение 2 ч усиливала антимикробные эффекты, наблюдающиеся при последовательном внесении растворов в лунки.

Ключевые слова: хитозан, энтеросорбент, антибактериальная активность, антибиотик, *Rhizopus oryzae*
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Introduction | Введение

One of the key areas in the advancement of medical biotechnology lies in the discovery and investigation of novel bioactive compounds with antimicrobial properties — a pursuit of particular relevance in light of the escalating issue of antibiotic resistance among pathogenic microorganisms. Chitosan, a promising candidate in this context, is a natural polysaccharide obtained via the deacetylation of chitin, the primary structural component of crustacean shells, insect exoskeletons, and fungal cell walls [5, 10, 16, 21].

Chitosan has attracted considerable scientific interest due to its biocompatibility, biodegradability, low toxicity, and pronounced sorptive and antimicrobial properties. These characteristics render it highly suitable for pharmaceutical, medical, and biotechnological applications, including its use as a drug delivery vehicle, a component of wound-healing dressings and scaffolds, and as an enterosorbent [5, 9, 10, 16, 20, 21, 24].

Fungi of the *Zygomycota* phylum, particularly *Rhizopus oryzae*, constitute one of the important alternative sources of chitosan. This microorganism is widely utilised in biotechnology owing to its ability to synthesise enzymes, organic acids, and antimicrobial compounds. Furthermore, the cell wall of *R. oryzae* contains a substantial amount of chitin-chitosan complex, making it a promising candidate for the production of chitosan of non-animal origin. Fungal chitosan offers several advantages over crustacean-derived chitosan, including reduced compositional variability, enhanced biocompatibility, and the potential for production under controlled cultivation conditions [4, 5, 18, 23].

Antibacterial agents are widely employed in contemporary medical practice and play a pivotal role in the treatment of infectious diseases. However, their use is often associated with the issue of drug-drug interactions, particularly when administered concurrently with sorbents or other biopolymers. Chitosan exhibits a high sorptive capacity, enabling it to bind not only toxic compounds but also active pharmaceutical ingredients, including antibiotics [5, 7, 10, 12, 20, 26]. Such interactions may either potentiate or diminish the antimicrobial efficacy of the drugs involved — a factor of considerable importance in clinical settings where combined therapies are employed.

Studies investigating the influence of chitosan on antibiotics have yielded conflicting results. In certain cases, chitosan has been shown to enhance antibiotic efficacy by facilitating their penetration into bacterial cells, particularly when low-molecular-weight forms are used. These smaller molecules are capable of interacting with cell membranes and increasing their permeability. Conversely, chitosan has also been reported to reduce

antibiotic activity, particularly in its high-molecular-weight forms, by adsorbing active molecules onto its surface and thereby decreasing their bioavailability [12, 17, 26, 29].

Chitosan exerts a similar influence on a range of other substances, including antifungal agents, metal ions, biologically active compounds, and dietary components. Low-molecular-weight chitosan has been shown to enhance the transport of nutrients and pharmaceutical agents across biological membranes, rendering it a promising candidate for the development of drug delivery systems. By contrast, high-molecular-weight chitosan displays pronounced adsorptive properties, which are exploited in detoxification systems, sorptive wound dressings, and dietary supplements. However, its strong binding capacity may adversely affect the bioavailability of beneficial compounds when administered orally [5, 10, 12, 29].

As a natural polymer, chitosan exhibits a broad spectrum of biological activities, among which its influence on antibiotic efficacy is of particular interest. This influence may manifest either as an enhancement or a reduction of antibacterial action, rendering the investigation of the underlying mechanisms critically important for the development of novel therapeutic strategies. The nature of this interaction is governed by multiple factors, including molecular weight, degree of deacetylation, chitosan concentration, environmental pH, the chemical structure of the antibiotics, and the susceptibility of the test microorganisms [7, 8, 17, 26].

The question of how chitosan affects antibiotic activity remains open, particularly in the context of developing new pharmaceutical formulations, medical devices, and functional supplements. The co-administration of chitosan with an antibiotic has the potential not only to enhance the antimicrobial activity of the latter, but also to impede the emergence and spread of resistance, as the two components operate via distinct mechanisms. This characteristic lends particular value to combined therapy in the context of combating antimicrobial resistance. Given that chitosan is predominantly utilised in oral formulations and as an enterosorbent, the present study addresses the potential of its complexes with antibiotics for enteral administration.

Although chitosan itself is not absorbed in the gastrointestinal tract, its mucoadhesive properties and ability to transiently open epithelial tight junctions can enhance the paracellular transport of co-administered drugs. In the chitosan/antibiotic complex, the polymer functions as a carrier and depot, retaining the antibiotic in the intestinal lumen while gradually releasing it for absorption.

Aim of the study | Цель работы — to evaluate the influence of chitosan on the activity of antimicrobial agents under *in vitro* conditions, to identify potential mechanisms of interaction, and to assess the feasibility of their combined use in medical practice.

In concordance with the aim, the objectives of the study were as follows: to investigate the effect of commercially available enterosorbents (Lactofiltrum®, Chitosan Evalar®, and Enterosgel®) on the activity of selected antibiotics (Amoxiclav®, Clarithromycin®, Cefoperazone®, and Ciprofloxacin-Teva®); to assess the impact of chitosan-based sorbents with varying molecular weights (MW) and degrees of deacetylation (DD) — including Chitosan Evalar®, chitosan from CJSC Bioprogress, BioChit® chitosan, and fungal chitosan derived from *Rhizopus oryzae* F-814 — on a set of antimicrobial agents comprising: ampicillin, vancomycin, gentamicin, kanamycin, clarithromycin, lomefloxacin, ofloxacin, and erythromycin; to evaluate the potential of chitosan as an adjuvant to antibiotic therapy.

Materials and Methods | Материалы и методы

Influence of enterosorbents on the in vitro activity of antimicrobial agents

Three enterosorbents — Lactofiltrum®, Chitosan Evalar®, and Enterosgel® — were test-

ed for their potential effects on the activity of four antimicrobial agents: Amoxiclav® (active ingredient (AI): amoxicillin), Clarithromycin® (AI: clarithromycin), Cefoperazone® (AI: cefoperazone), and Ciprofloxacin-Teva® (AI: ciprofloxacin).

The antibiotics used in this study included both commercial formulations and pure active pharmaceutical ingredients (APIs). Amoxiclav (film-coated tablets, 875 mg/125 mg, Sandoz, Austria) and ciprofloxacin (film-coated tablets, 500 mg, Teva Pharmaceutical Industries Ltd., Hungary) were employed in their commercial dosage forms. Clarithromycin and cefoperazone were obtained as pure APIs from the Department of New Technologies, Pasteur Research Institute of Epidemiology and Microbiology (Saint Petersburg, Russian Federation).

The activity of the antibiotics was assessed using six test strains from the microbial collection of the Department of Microbiological Synthesis Technology at Saint Petersburg State Institute of Technology (Technical University). These included *Escherichia coli* (Gram-negative (Gr^-), non-spore-forming (Sp^-)), *Bacillus cereus* (Gram-positive (Gr^+), spore-forming (Sp^+)), *Staphylococcus citreus* (Gr^+, Sp^-), *Bacillus subtilis* (Gr^+, Sp^+), *Micrococcus polychromus* (Gr^+, Sp^-), and *Pseudomonas putida* (Gr^-, Sp^-). This selection enabled the evaluation of drug effects on bacteria with diverse cell wall structures and membrane permeability profiles. The chosen strains were selected based on their availability, phenotypic stability, and biosafety under standard laboratory conditions, as well as their suitability for standardised experimental procedures.

The test cultures were maintained on slant agar (GRM agar) in test tubes at 4−6°C. Subculturing was carried out periodically, once every 2–3 months.

Antimicrobial activity was assessed using the agar well diffusion method on GRM agar. Inoculum were prepared from 24-hour microbial cultures and adjusted to a turbidity equivalent to 0.5 on the McFarland scale.

The composition of the GRM agar (per litre) was as follows: enzymatic hydrolysate of fishmeal — 12 g; fermentative peptone — 12 g; NaCl — 6 g; microbiological agar — 20 g; tap water — up to 1 L; final pH — 7.1 to 7.5. The medium was sterilised by autoclaving at 76 kPa for 30 minutes, then poured into sterile Petri dishes to a depth of 4 mm.

In a previous study [2], we established that the method of administration — either sequential addition or pre-mixing — did not affect the activity of ciprofloxacin in the presence of chitosan. Furthermore, experiments conducted at varying pH values (7.9 and 2.5) revealed no statistically significant effect of medium acidity on the interaction between ciprofloxacin and chitosan, nor on the antibiotic's intrinsic activity. Based on these findings, the sequential administration method was adopted for the present study.

The pH of the medium was adjusted to 7.9 in all experiments. This value was selected to model the upper physiological range of intestinal pH. According to [28], pH in the small intestine of healthy individuals ranges from 6.4 to 7.4 (median 6.9), while distal segments of the large intestine may reach up to 8.2. The review [27] further confirms that pH in the distal small intestine averages approximately 7.5 and may increase to 7.8 in the large intestine. In addition, study [1] reports a range of 7.0–8.0 as characteristic of the small intestine.

A slightly alkaline environment supports the stability and solubility of many antibiotic classes, including fluoroquinolones and macrolides, while significant degradation is typically observed only under conditions far beyond the physiological range. Moreover, a pH of 7.9 optimises the binding of antibiotics to the chitosan matrix, providing a more accurate *in vitro* simulation of conditions relevant to enteral administration. Therefore, a pH of 7.9 was chosen as a model value approximating the upper physiological boundary, ensuring

both the stability of the antibiotics and reliable assessment of their interaction with chitosan.

To ensure physiologically relevant *in vitro* conditions, the concentrations of antibiotics were selected to approximate their average plasma levels following enteral absorption, whereas the concentrations of enterosorbents (which are not systemically absorbed) were calculated in concordance with recommended therapeutic dosages to simulate their action within the intestinal lumen.

Working solutions of the antibiotics were prepared at the following AI concentrations, μg/mL: Amoxiclav® — 40; Clarithromycin® — 200; Cefoperazone® — 20; Ciprofloxacin® — 20. The enterosorbents were prepared at the following concentrations, mg/mL: Lactofiltrum® — 35 and 70; Chitosan Evalar® — 20, 40, and 80; Enterosgel® — 75 and 150.

The tablets were finely ground using a mortar and pestle prior to solution preparation, and the required amounts of ground tablets and API powders were dissolved in sterile distilled water. The working antibiotic solutions were prepared in sterile 10 mL glass penicillin vials, each filled to 6 mL. The enterosorbent solutions were prepared in the same manner, with the required amounts of each enterosorbent dissolved in sterile distilled water at the specified concentrations. The pH of each solution was then adjusted to the required level using 0.1 M sodium hydroxide.

It is vital to mention the stability of the antibiotics at pH 7.9. Amoxicillin retains more than 90% of its initial concentration after 24 h at pH 7–8 in aqueous solution at 37°C [22]. Ciprofloxacin is also stable within this pH range: according to [13], only moderate degradation is observed between pH 7 and 8 (approximately 84–93% of the initial content remains). Data from [25] further confirm that ciprofloxacin shows no significant degradation at pH 4–7 under dark conditions for up to 72 h, with pH-dependent photodegradation occurring only under simulated light. Clarithromycin remains relatively stable in slightly alkaline environments: photodegradation studies indicate that at pH 7.0 less than 20% of the compound degraded after 1 h of simulated sunlight, and its stability improves slightly at higher pH values [25]. Finally, cefoperazone shows stable activity between pH 6.4 and 8.0, as confirmed by *in vitro* tests, with no loss of efficacy across this pH range [19]. Therefore, under experimental conditions employed (pH 7.9, 37°C, 48 h, absence of intense light), these antibiotics are unlikely to undergo substantial hydrolysis or inactivation.

Following solidification of the agar plates, 100 μL of the prepared microbial inoculum was applied to the surface and evenly distributed using a sterile spreader. Once the surface was dry, five wells were aseptically bored into the agar (per Petri dish) using a sterile drill. In three of the wells, solutions of antibiotic and enterosorbent were added sequentially at the specified concentrations. Wells 4 and 5 served as controls: well 4 received the antibiotic alone (AI concentrations, μg/mL: amoxicillin — 40; clarithromycin — 200; cefoperazone — 20; ciprofloxacin — 20), and well 5 received the enterosorbent alone (mg/mL: Lactofiltrum® — 70; Chitosan Evalar® — 80; Enterosgel® — 150). Plates were incubated at 37±1°C for 48 hours, after which the diameters of microbial growth inhibition zones were measured in millimetres (mm).

Effect of chitosan-containing sorbents on the activity of antibacterial agents

The study employed three types of crab-derived chitosan: Chitosan Evalar® (MW: not specified; DD: 75%), low-molecular-weight (LMW) chitosan from BioChit Research and Production Centre CJSC (MW: 50 kDa; DD: 85.0%), and medium-molecular-weight (MMW) chitosan from Bioprogress CJSC (MW: 83.7 kDa; DD: 89.0%).

The effect of chitosan on the activity of antibiotics from various pharmacological classes was investigated. The tested agents included: ampicillin (AMP; penicillins), vancomycin

(VAN; tricyclic glycopeptides), gentamicin and kanamycin (GEN and KAN, respectively; aminoglycosides), clarithromycin (CLA; macrolides), ofloxacin and lomefloxacin (OFL and LOM, respectively; fluoroquinolones), and erythromycin (ERY; macrolides). The antibiotics were provided by the Department of New Technologies at the Pasteur Institute of Epidemiology and Microbiology (Saint Petersburg, Russian Federation).

The bacterial cultures used in this study were *Escherichia coli* and *Bacillus cereus*, obtained from the collection of the Department of Microbiological Synthesis Technology at Saint Petersburg State Institute of Technology (Technical University).

Antimicrobial activity was assessed using the agar well diffusion method on GRM agar. The medium and inoculum were prepared as described previously.

In three of the wells, 100 µL of the antibiotic-chitosan sorbent solution was added. Wells 4 and 5 served as controls, containing the antibiotic alone at a concentration of 500 µg/mL and chitosan alone at 40 mg/mL, respectively.

Stock solutions of the test substances were prepared by dissolving the required quantities in distilled water, followed by ultrasonic treatment for 15 minutes. Antibiotics were applied at concentrations of 10 and 100 µg/mL, while chitosan-containing sorbents were used at a concentration of 40 mg/mL.

Incubation was carried out at 37±1°C for 24–48 h. Antimicrobial activity was evaluated by measuring the diameters of bacterial growth inhibition zones (in mm).

For antibiotics to which the bacterial cultures exhibited resistance, the minimum inhibitory concentration (MIC) was determined using the broth microdilution method in 96-well plates, with GRM medium as the growth substrate.

The composition of GRM medium (*per litre*) was as follows: enzymatic hydrolysate of fishmeal — 12 g; fermentative peptone — 12 g; NaCl — 6 g; tap water — up to 1 L; final pH — 7.1 to 7.5. The medium was sterilised by autoclaving at 76 kPa for 30 minutes and then dispensed into sterile microplates. Serial dilutions of antibiotics were prepared at the following concentrations (µg/mL): 500, 250, 125, 62.5, and 31.25. The inoculum was prepared as described above. Three control wells were included: (1) GRM medium only; (2) GRM medium with inoculum; and (3) GRM medium with inoculum and antibiotic at 800 µg/mL. Plates were incubated under the same conditions as described previously. MIC values were assessed visually.

Effect of fungal chitosan on the activity of antimicrobial agents

The activity of high-molecular-weight (HMW) chitosan derived from the fungus *Rhizopus oryzae* F-814 (MW: 400 kDa; DD: 86.8%) was investigated [3, 11, 14]. The strain *Rhizopus oryzae* F-814, also known as ATCC 9363, NRRL 395, and IMI 40564, was obtained from the National Bioresource Centre "All-Russian Collection of Industrial Microorganisms". It is classified as safe and authorised for use in the food, pharmaceutical, and related industries [15]. The strain is cultivated and maintained on potato-glucose agar at the Department of Microbiological Synthesis Technology, Saint Petersburg State Institute of Technology (Technical University).

Potato-glucose agar and potato-glucose broth were prepared in accordance with the method described in [6].

The antimicrobial agents tested included ampicillin, kanamycin, clarithromycin, and ofloxacin. The test cultures used were *Escherichia coli* and *Bacillus cereus.*

The effect of chitosan on antibiotic activity was evaluated using two different administration methods: sequential addition (as described earlier) and pre-sorption of antibiotics onto chitosan.

Antibiotic and chitosan samples were prepared as previously described, at concentrations of 100 µg/mL and 10 mg/mL, respectively.

For pre-sorption, 1 mL of chitosan solution (10 mg/mL) and 1 mL of antibiotic solution (100 μg/mL) were added to 8 mL of sterile distilled water in a sterile test tube. The mixture was agitated using a shaker (ES-60, MIULAB, Hangzhou Miu Instruments CO., LTD, People's Republic of China) at 300 rpm and 25±2°C for 2 hours. Following incubation, the supernatant was decanted and used for the agar well diffusion assay (applied volume: 100 μL).

The antimicrobial activity of the antibiotics and chitosan samples was assessed using the agar well diffusion method on GRM agar, as previously described. After 48 hours of incubation at 37±1°C, the diameters of microbial growth inhibition zones were measured in mm.

Results and Discussion | Результаты и их обсуждение

Investigation of the *in vitro* effect of enterosorbents on the activity of antimicrobial agents

The *in vitro* interaction between antimicrobial agents and enterosorbents was investigated to assess the potential impact of sorbents on antibiotic efficacy and to identify possible limitations associated with their concurrent use.

Laboratory strains of *Escherichia coli* and *Bacillus cereus*, both susceptible to several of the tested agents, were used in the experiment. Although this selection does not encompass the full range of bacterial pathogens and excludes clinical isolates, it enables a preliminary assessment of the potential influence of enterosorbents on antibiotic activity. The choice of antimicrobial agents was based on the information provided in their official prescribing guidelines and corroborated by published scientific literature, indicating their efficacy against the bacterial species used in this study.

No statistically significant effect of Lactofiltrum®, Chitosan Evalar®, or Enterosgel® on the antimicrobial activity of ciprofloxacin, amoxiclav, clarithromycin, or cefoperazone was observed in the conducted experiments. These findings suggest that the tested enterosorbents do not induce meaningful alterations in the pharmacological efficacy of the specified antibiotics when used in combination *in vitro*.

Chitosan Evalar® and Enterosgel® exhibited no antimicrobial activity against *Escherichia coli, Bacillus cereus, Staphylococcus citreus, Bacillus subtilis, Micrococcus polychromus*, or *Pseudomonas putida.* However, Lactofiltrum®, at a concentration of 70 mg/mL, demonstrated antibacterial activity against *Staphylococcus citreus*, with a growth inhibition zone measuring 14±1 mm. This finding suggests the presence of additional properties in the preparation that warrant further investigation. The observed effect may be attributed to specific components within the formulation that influence the growth characteristics of certain microbial species.

The results obtained are consistent with published data on the mechanisms of action of enterosorbents, which indicate that they should not exert a significant effect on the activity of antimicrobial agents in the absence of specific binding to the active pharmaceutical ingredients. This is further supported by the observation that the microbial growth inhibition zones observed during combined application of antibiotics and enterosorbents did not differ from the control values.

Analysis of the effect of chitosan-containing sorbents on the activity of antibacterial agents

The effect of chitosan-containing sorbents on the activity of antibacterial agents was assessed against *Bacillus cereus* (Table 1) and *Escherichia coli* (Table 2). In addition, a key objective was to investigate the direct impact of the chitosan-containing sorbents on the growth of the test cultures. This allowed for the identification of any intrinsic antimicrobial activity of the sorbents themselves and provided further insight into their potential influence on the growth dynamics of bacterial cells.

BioChit® chitosan (MM: 50 kDa; DD: 85%) predominantly enhanced the activity of antibiotics, particularly against *Bacillus cereus*. This effect may be attributed to its

Table 1. *Changes in antibiotic activity against Bacillus cereus, %*
Таблица 1. *Изменение активности антибиотиков в отношении Bacillus cereus, %*

Antibiotic, μg/mL		Chitosan Evalar®	Bioprogress®	BioChit®
GEN	10	− 14.5	− 10.3	+ 12.5
	100	− 18.2	− 17.2	+ 15.7
KAN	10	not observed	not observed	observed
	100	remains unchanged	− 13.0	+ 21.7
CLA	10	− 21.2	− 12.1	+ 10.8
	100	− 20.0	− 26.7	+ 16.7
LOM	10	− 25.0	− 12.5	+ 20.0
	100	− 17.2	− 24.1	+ 24.6
OFL	10	− 12.5	− 8.3	+ 11.1
	100	− 14.3	− 20.0	+ 13.4

Note: *"−" and "+" denote a decrease and increase by the specified value, respectively.*
Примечание: *«−»уменьшение на X; «+» — увеличение на Y.*

Table 2. *Changes in antibiotic activity against Escherichia coli, %*
Таблица 2. *Изменение активности антибиотиков в отношении Escherichia coli, %*

Antibiotic, μg/mL		Chitosan Evalar®	Bioprogress®	BioChit®
AMP	10	− 8.3	− 5.5	remains unchanged
	100	− 7.1	remains unchanged	
GEN	10	− 9.3	− 12.1	remains unchanged
	100	− 12.0	− 15.5	
KAN	10	remains unchanged	remains unchanged	remains unchanged
	100			
CLA	10	remains unchanged	remains unchanged	remains unchanged
	100	− 9.4	− 9.4	
LOM	10	− 8.7	− 21.7	remains unchanged
	100	− 10.0	− 12.5	
OFL	10	remains unchanged	− 10.0	remains unchanged

low molecular weight, which facilitates penetration through the bacterial cell envelope or interaction with its surface. It is also possible that chitosan disrupts cell wall integrity and increases membrane permeability, thereby promoting the intracellular uptake of the antibiotic.

Bioprogress® chitosan (MM: 83.7 kDa; DD: 89%) was more frequently associated with a reduction in antibiotic activity. This effect is likely due to several factors: adsorption of antibiotics onto the surface of chitosan molecules, facilitated by its extended polymer structure; a consequent decrease in the free concentration of the antibiotic in the medium (particularly for LMW agents); and the potential formation of insoluble complexes or physical entrapment of antibiotics by the chitosan matrix.

Chitosan Evalar® (MW: not specified; DD: 75%) exhibited a moderate inhibitory effect on antibiotic activity, which is likely attributable to its low degree of deacetylation. This would reduce the number of available amino groups involved in ionic interactions and sorption processes.

The MMW chitosan Bioprogress® predominantly exerted an inhibitory effect on the activity of most of the tested antibiotics against both *Bacillus cereus* and *Escherichia coli.*

The most pronounced reduction in activity was observed with fluoroquinolones — ofloxacin and lomefloxacin — against *B. cereus*, with decreases of 26.7% and 24.1%, respectively. In the case of *E. coli*, a marked reduction in efficacy was noted for gentamicin (aminoglycoside) and erythromycin (macrolide), with activity decreasing by 2-fold and 8-fold, respectively, compared with the control.

This effect may be attributed to the sorptive properties of chitosan, which are particularly pronounced at high MW. The extended polymer structure facilitates active absorption of antibiotics from the surface of the medium. Ionic interactions between the positively charged amino groups of chitosan (especially at high degrees of deacetylation) and anionic or neutral antibiotic molecules may lead to the formation of complexes that reduce the antibiotic's availability to bacterial cells. Additionally, the observed decrease in antimicrobial activity may result from physical entrapment of the antibiotic by the chitosan macromolecule, reduced diffusion through the agar medium, and/or impaired penetration across the bacterial cell wall.

Interestingly, in the case of vancomycin against *E. coli*, the opposite effect was observed — antibiotic activity increased twofold. This may be due to the ability of MMW chitosan to transiently disrupt the barrier properties of the outer membrane in Gram-negative bacteria, thereby increasing permeability and facilitating the intracellular uptake of the antibiotic.

It was found that ampicillin, vancomycin, and erythromycin (at concentrations of 10 and 100 μg/mL), as well as kanamycin (at 10 μg/mL), did not inhibit the growth of *Bacillus cereus*. Therefore, their minimum inhibitory concentrations (MICs, μg/mL) were determined: AMP — 150; VAN — 250; KAN — 50; ERY — 250. The addition of Bioprogress® chitosan was shown to influence the antimicrobial activity against this strain, reducing the activity of ampicillin and vancomycin by twofold, while the activity of kanamycin and erythromycin remained unchanged.

For *Escherichia coli*, the following minimum inhibitory concentrations (MICs, μg/mL) were established: VAN — 125; ERY — 250. It was observed that the addition of Bioprogress® chitosan reduced the antimicrobial activity of erythromycin eightfold. In contrast, vancomycin activity increased twofold, which may be attributed to enhanced membrane permeability in the presence of chitosan.

The results of this study demonstrate that the effect of chitosan-containing sorbents on antibiotics is influenced by their molecular weight and chemical structure. Medium- and high-MW forms of chitosan tend to reduce antibiotic activity, likely due to sorption mechanisms. In contrast, LMW chitosan not only exhibits intrinsic antimicrobial properties but also enhances the efficacy of certain antibiotics, particularly against Gram-positive bacteria. These findings highlight the need for further investigation into the mechanisms underlying chitosan-antibiotic interactions, with a view to their potential application in clinical practice. Such differences should be carefully considered in the development of combination therapies and in cases where antibiotics are co-administered with enterosorbents.

Investigation of the effect of fungal chitosan on the activity of antimicrobial agents

In the assessment of antimicrobial activity, the fungal chitosan solution derived from *Rhizopus oryzae* F-814 (10 mg/mL) exhibited inhibitory effects against *Bacillus cereus*, *Escherichia coli*, and *Staphylococcus citreus*. The diameters of the growth inhibition zones were (mm): 29.5±1.5, 21.0±1.0 and 31.0±1.0, respectively.

The effect of HMW chitosan on antibiotic activity was assessed using both sequential administration into the agar wells and pre-sorption of antibiotics onto the chitosan matrix, across various microbial species (Table 3).

Table 3. *Effect of fungal chitosan on the efficacy of antibiotics, %*
Таблица 3. *Влияние грибного хитозана на эффективность антибиотиков, %*

Antibiotic, μg/mL	Sequential addition			Pre-sorption		
	B. cereus	*E. coli*	*S. citreus*	*B. cereus*	*E. coli*	*S. citreus*
AMP	R	R	+ 8.1	R	R	+ 6.2
CLA	− 6.0	− 2.8	− 3.6	− 34.4	− 16.4	− 20.7
KAN	R	+ 20.5	R	R	+ 72.7	R
OFL	+ 30.6	+ 25.4	+ 30.0	+ 36.5	+ 57.1	+ 34.7

Note: *"R" — resistant.*
Примечание: *«R» — сопротивление.*

The analysis of the effect of HMW fungal chitosan on the antimicrobial activity of various antibiotics revealed that the nature of the interaction depends on both the method of application (sequential addition or pre-sorption) and the specific combination of antibiotic and microbial species.

It was noted that HMW chitosan did not exert a significant effect on the activity of ampicillin.

Clarithromycin exhibited reduced activity against all three test cultures following the addition of fungal chitosan, with the effect being particularly pronounced after pre-sorption. A likely mechanism involves the adsorption of the macrolide onto the polysaccharide matrix, which decreases its bioavailability and diffusion within the growth medium.

B. cereus and *S. citreus* remained resistant to kanamycin under all tested conditions; however, *Escherichia coli* exhibited a marked increase in susceptibility: +20.5% following sequential addition and +72.7% after pre-sorption. This may indicate a synergistic interaction between fungal chitosan and aminoglycosides, potentially mediated by increased membrane permeability or enhanced intracellular transport of the antibiotic.

The most pronounced positive interaction was observed with ofloxacin, whose activity increased by 25.4–57.1% across all experimental conditions and against all tested bacterial strains. The effect was particularly evident following pre-sorption: +36.5% for *B. cereus*, +57.1% for *E. coli*, and +34.7% for *S. citreus*. This enhancement may be attributed to a stabilising effect of chitosan on the antibiotic molecules, or to potentiation of fluoroquinolone penetration through the bacterial cell wall, possibly mediated by interactions with surface components of the bacterial envelope.

Pre-sorption of antibiotics onto chitosan enhanced both the positive (KAN, OFL) and negative (CLA) effects compared to sequential addition of the solutions into the wells, indicating an active role of HMW chitosan in modulating antibiotic availability.

The differences in the effects of HMW chitosan on microorganisms, compared to the experiments described in the previous section, may be attributed to variations in MW, DD, molecular geometry, the origin of the chitosan used, and other contributing factors.

Chitosan with a MW of 400 kDa forms longer and more highly branched polymer chains, characterised by high viscosity and the ability to form gel-like structures. This may result in the encapsulation of antibiotic molecules, particularly under pre-sorption conditions, thereby leading either to reduced bioavailability or to delayed release with a sustained effect. At the same time, such structures may stabilise antibiotics under harsh conditions and promote their diffusion into bacterial cells — provided that the degree of sorption is not excessive, as exemplified by the case of ofloxacin.

Although both chitosans possess amino groups and a similar degree of deacetylation, the larger molecules (400 kDa) may exhibit

a higher overall sorption capacity — but not necessarily greater specificity. Chitosan with a MW of 83.7 kDa is less branched and may more effectively retain antibiotics on its surface, thereby reducing their activity by preventing their release, particularly under conditions of sequential administration.

Fungal chitosan (400 kDa) may also form semi-colloidal systems that distribute the antibiotic differently compared to the more "soluble" and mobile 83.7 kDa chitosan. Such differences influence the diffusion of the antibiotic through the agar medium and, consequently, affect the size of the inhibition zones.

In addition to molecular weight, chitosan derived from *R. oryzae* differs in chain conformation, purity level, and even surface charge. These characteristics may either enhance or weaken its interactions with specific antibiotics — such as macrolides (e.g., clarithromycin) — resulting in either reduced activity or potentiation of the antimicrobial effect.

The findings confirm that the interaction between chitosan and antibiotics cannot be regarded as a passive physical coexistence within the medium. On the contrary, chitosan is capable of actively modulating the behaviour of antibiotic molecules by altering their spatial distribution, free concentration, and availability for interaction with bacterial cells. Owing to its functional groups — primarily cationic amino groups — chitosan can engage in ionic, hydrogen bonding, and hydrophobic interactions with antibiotics, thereby influencing molecular stability, bioavailability, cell wall permeability, and delivery mechanisms. Thus, chitosan plays an active modulatory role within such systems, impacting the pharmacodynamics of antibiotics even *in vitro*, which is particularly important to consider in the development of combined therapeutic formulations.

The results underscore the necessity of a differentiated approach when selecting sorbents and antibiotics for combined use, particularly in clinical therapy. The application of chitosan in combination with antibiotics requires careful consideration of its physicochemical properties, the mechanisms of interaction with drug molecules, and the structural features and susceptibility profiles of the target microorganisms.

Conslusion | Заключение

The enterosorbents Lactofiltrum®, Chitosan Evalar®, and Enterosgel® did not exhibit a significant effect on the activity of the tested antibiotics — amoxicillin, clarithromycin, ciprofloxacin, and cefoperazone.

Chitosan Evalar® (40 mg/mL) demonstrated inhibitory effects at both 10 and 100 µg/mL concentrations against gentamicin, clarithromycin, lomefloxacin, and ofloxacin in *Bacillus cereus*, as well as ampicillin, gentamicin, lomefloxacin, and ofloxacin (only at 10 µg/mL) in *Escherichia coli*.

Low-molecular-weight chitosan (MW: 50 kDa; DD: 85%) enhanced the efficacy of gentamicin, kanamycin, clarithromycin, lomefloxacin, and ofloxacin against *B. cereus*.

Medium-molecular-weight crab chitosan (MW 83.7 kDa; DD 89%) reduced the activity of fluoroquinolone antibiotics (lomefloxacin and ofloxacin at both 10 and 100 µg/mL) by 8.3–24.1% against *B. cereus* and *E. coli*.

High-molecular-weight fungal chitosan (MW: 400 kDa; DD: 86.8%) derived from *Rhizopus oryzae* F-814 (at 40 mg/mL) inhibited the growth of *Escherichia coli*, *Bacillus cereus*, and *Staphylococcus citreus*. In addition, fungal chitosan enhanced the activity of kanamycin and ofloxacin following pre-sorption and reduced the activity of clarithromycin.

It is worth noting that the materials with molecular weights of 83.7 kDa and 400 kDa, although both formally classified as high-molecular-weight forms of chitosan, exhibit fundamentally different behaviours in *in vitro* biological models. These differences are attributable not only to the absolute molecular

weight but also to a combination of functional characteristics that determine the actual activity of the substance in solution and in its interaction with antibiotics.

Thus, when selecting chitosan for medical and biotechnological applications, it is advisable to consider not only its molecular weight but also a comprehensive set of functional parameters, including: polydispersity; solubility at physiological pH; chain architecture; intrinsic viscosity and gel-forming capacity; surface charge and ion-exchange potential (as determined by the degree of deacetylation); degree of crystallinity/ amorphousness; particle size and morphology; origin and purity (animal- or fungal-derived, presence of copolymers or impurities); and thermal stability.

A comprehensive assessment of these properties will enable more accurate prediction of chitosan's behaviour within pharmaceutical formulations, including its impact on antibiotic bioavailability, sorptive activity, and potential synergistic or antagonistic effects.

The findings highlight the necessity of an integrated approach to evaluating the combined use of antibiotics and polysaccharide-based sorbents in the development of combined therapeutic strategies.

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