DOI: https://doi.org/10.17816/RCF624703
Review Article

Pharmacological efficacy and potential of the use of nitazoxanide, a thiazolide drug with a wide spectrum of action

Vladimir V. Rusanovsky, Anastasiya A. Saveleva, Zara G. Tadtaeva, Egor S. Astudin, Aleksandr E. Krivoshein, Aleksandr A. Akimov, Natalia A. Kuritsina

Saint Petersburg State Pediatric Medical University, Saint Petersburg, Russia

ABSTRACT

The article is devoted to the possibility and prospects of using nitazoxanide in a wide range of diseases. Based on literature data, the authors evaluate the pharmacological effectiveness and substantiate the potential of using nitazoxanide in bacterial, helminthic, protean, viral and oncological diseases. This information is of interest and can be used to decide on the need to conduct clinical trials of nitazoxanide in Russia. A systematic search for current information was conducted in four databases until December 1, 2023: PubMed, EMBASE, Web of Science and Cochrane Library. The work included preclinical studies *in vitro* and *in vivo*, as well as randomized clinical trials comparing the pharmacological effectiveness of nitazoxanide and placebo. The broad-spectrum thiazolide drug nitazoxanide has antibacterial, antiprotozoal, anthelmintic, antiviral and antitumor activity. This is achieved through its pharmacological properties, namely: regulation of the cell cycle, apoptosis, cell proliferation and migration; activation of innate immunity; influence on the synthesis and activation of cell proteins, some of which are links in cellular signaling pathways; binding to proteins of viruses, bacteria, protozoa and helminths with disruption of their vital functions; immunomodulating effect by regulating the activity of pro- and anti-inflammatory cytokines. The article systematizes and summarizes current information on the pharmacodynamics of nitazoxanide, as well as the results of preclinical and clinical studies of the drug, and discusses further prospects.

Keywords: nitazoxanide; thiazolides; thiazoxanide; antiviral; anthelmintics; antiprotozoal; antibacterial; antitumor.

To cite this article

Rusanovsky VV, Saveleva AA, Tadtaeva ZG, Astudin ES, Krivoshein AE, Akimov AA, Kuritsina NA. Pharmacological efficacy and potential of the use of nitazoxanide, a thiazolide drug with a wide spectrum of action. *Reviews on Clinical Pharmacology and Drug Therapy*. 2024;22(1):81–96. DOI: https://doi.org/10.17816/RCF624703

Received: 16.12.2023 **Accepted:** 28.02.2024 **Published:** 29.03.2024

УДК 616.1
DOI: https://doi.org/10.17816/RCF624703
Обзорная статья

Оценка фармакологической эффективности и потенциала применения нитазоксанида — препарата тиазолидного ряда широкого спектра действия

В.В. Русановский, А.А. Савельева, З.Г. Тадтаева, Е.С. Астудин, А.Е. Кривошеин, А.А. Акимов, Н.А. Курицына

Санкт-Петербургский педиатрический медицинский университет, Санкт-Петербург, Россия

АННОТАЦИЯ

Статья посвящена возможности и перспективе применения нитазоксанида при широком спектре болезней. На основании литературных данных авторы оценивают фармакологическую эффективность и обосновывают потенциал применения нитазоксанида при бактериальных, гельминтных, протейных, вирусных и онкологческих заболеваниях. Эта информация представляет интерес и может быть использована для принятия решения о необходимости проведения клинических испытаний нитазоксанида на территории России. Систематический поиск актуальной информации в четырех базах данных: PubMed, EMBASE, Web of Science и Cochrane Library проводили до 1 декабря 2023 г. Работы включали доклинические исследования *in vitro* и *in vivo*, а также рандомизированные клиническими исследования, сравнившие фармакологическую эффективность нитазоксанида и плацебо. Препарат тиазолидного ряда широкого спектра действия нитазоксанид обладает антибактериальной, противопротозойной, антигельминтной, противовирусной и противоопухолевой активностью. Это достигается посредством его фармакологических свойств: регуляции клеточного цикла, апоптоза, пролиферации и миграции клеток; активирования звеньев врожденного иммунитета; влияиния на синтез и активацию белков клетки, часть которых — звенья клеточных сигнальных путей; связывания с белками вирусов, бактерий, простейших и гельминтов с нарушением их жизнедеятельности; иммуномоделирующего действия путем регуляции активности про- и противовоспалительных цитокинов. В статье систематизированы и обобщены актуальная информация о фармакодинамике нитазоксанида, а также результаты доклинических и клинических исследований препарата, рассмотрены дальнейшие перспективы.

Ключевые слова: нитазоксанид; тиазолиды; тиазоксанид; противовирусные; антигельминтные; противопротозойные; антибактериальные; противоопухолевые.

Как цитировать

Русановский В.В., Савельева А.А., Тадтаева З.Г., Астудин Е.С., Кривошеин А.Е., Акимов А.А., Курицына Н.А. Оценка фармакологической эффективности и потенциала применения нитазоксанида — препарата тиазолидного ряда широкого спектра действия // Обзоры по клинической фармакологии и лекарственной терапии. 2024. Т. 22. № 1. С. 81–96. DOI: https://doi.org/10.17816/RCF624703

Рукопись получена: 16.12.2023 **Рукопись одобрена:** 28.02.2024 **Опубликована:** 29.03.2024

ЭКО•ВЕКТОР

INTRODUCTION

Nitazoxanide (NTZ), the first thiazolid, was discovered by French scientists Jean-François Rossignol and Raymond Cavier in 1974. In 1976, they patented new derivatives of 2-benzamido 5-nitrothiazoles, which exhibited antiparasitic and fungicidal effects [1]. In 1984, Rossignol published an article in the *American Journal of Tropical Medicine & Hygiene*, which described the effect of NTZ on patients infected with *Taenia saginata* and *Hymenolepis nana* [2]. Subsequently, studies of NTZ against cryptosporidial diarrhea in patients with HIV infection were conducted in the USA in collaboration with Romark Laboratories and Unimed Pharmaceuticals [3]. However, because of issues with enrolment and study methodology, the US Food and Drug Administration rejected the application for accelerated approval of this drug [4]. In 2003, NTZ was demonstrated to be efficacious in the treatment of cyclosporiasis, isosporiasis, and amebiasis [5], and in 2007, the *International Journal of Infectious Diseases* corroborated its effectiveness against *Taenia saginata* [6]. In 2011, the successful use of NTZ in conjunction with vancomycin was documented in a patient with recurrent *Clostridium difficile* infection [7].

The need for new drugs has become increasingly urgent because of the discovery of new viruses and parasites and the increasing problem of antibiotic resistance [8]. In recent years, the interest in NTZ as a potential candidate drug for this role has increased, which is reflected in the exponential growth in the number of studies investigating its mechanisms of action, reporting promising results [9, 10]. Moreover, recent studies have demonstrated the antitumor activity of NTZ, which may have a profound effect on the efficacy of cancer treatment in the future [11].

Currently, NTZ is used in the USA under the brand name Alinia® as oral suspension (for patients aged ⩾1 year) and tablets (for patients aged ⩾12 years) for the treatment of diarrhea caused by *Giardia lamblia* or *Cryptosporidium parvum* [12]. The drug is not registered in Russia.

ANTIPROTOZOAL ACTIVITY

NTZ exhibits antiprotozoal activity by interfering with the pyruvate-ferredoxin/flavodoxin oxidoreductase-dependent electron transfer reaction, which is required for the anaerobic energy metabolism of various microorganisms. The growth of sporozoites and trophozoites is inhibited consequently, which alleviates diarrhea. Furthermore, NTZ induces cell membrane damage and mitochondrial membrane depolarization in parasitic protozoa while inhibiting quinone oxidoreductase, nitroreductase 1, and protein disulfide isomerase [13]. In an *in vitro* study, the effect of NTZ on the ultrastructure of trophozoites included swelling of cells and distortion, vacuole redistribution, plasma membrane damage, and formation of extensive empty areas in the cytoplasm of protozoa [14]. In a systematic review and meta-analysis of randomized controlled clinical trials of NTZ in the treatment of intestinal infections, including those caused by protozoa, M.R. Hashan et al. [15] present the data in Table 1. Clinical trials have demonstrated the efficacy of NTZ in the treatment of cryptosporidiosis and giardiasis, including in immunocompromised patients and patients aged <12 years [16–18]. However, further studies are required to substantiate this assertion [19]. In multiple studies, NTZ exhibited high activity against amebiasis pathogens in comparison with the placebo and metronidazole [20–22]. In addition, NTZ administration was reported to be associated with a significantly lower incidence of adverse events than metronidazole therapy [22]. This was demonstrated in a clinical study involving 60 patients with amebiasis accompanied by liver abscesses (Table 2). Group M received metronidazole at 2–2.5 g/day intravenously in an inpatient setting or 2–2.4 g/day orally for outpatients three times daily for 14 days. Group N received NTZ at 500 mg twice daily orally for 10 days. In that study, the adverse event rates were significantly higher in group M than in group N.

Table 1. Effectiveness of nitazoxanide against parasitic protozoa

Таблица 1. Эффективность нитазоксанида в отношении паразитических простейших

Species	*In vivo* efficacy of nitazoxanide
Giardia lamblia	High significant response compared with placebo, metronidazole, and tinidazole with (95% CI 1.08–2.64; $p = 0.27$)
Entamoeba hystolitica	Effective compared with placebo (95% CI 1.35–2.40; $p < 0.001$)
Cryptosporidium parvum	Effective compared with placebo (95% CI 1.22–1.74; $p < 0.0001$)

Table 2. Effectiveness of nitazoxanide against amoeba compared with metronidazole

Таблица 2. Эффективность нитазоксанида в отношении паразитических простейших

Indicators	Group M (metronidazole)	Group H (nitazoxanide)	*p*
Symptomatic clinical response	80%	76.70%	0.1
Complete solution of the abscess in 6 months	60%	73.30%	0.273

ANTIHELMINTHIC ACTIVITY

In nematodes, NTZ inhibits glutathione-S-transferase, a key detoxification enzyme, resulting in the loss of resistance to certain drugs and human immune protective factors [13, 23]. NTZ also modulates *Avr 14*, which encodes the alpha-type subunit of the glutamate-regulated chloride ion channel. This results in the formation of substrates for antiparasitic drugs of the avermectin family, which increases their efficacy. Avermectins enhance the effect of glutamate on invertebrate-specific ion channels, causing hyperpolarization and paralysis of invertebrate neuromuscular systems [13, 24, 25]. *In vitro* NTZ demonstrated efficacy as a synergist of avermectin family of anthelmintics. Clinical studies have corroborated the effectiveness of NTZ against *Hymenolepis nana* [26] and other soil-transmitted nematodes [27, 28]. Numerous clinical cases have also been documented for the treatment of patients with echinococcosis who had previously failed conservative and surgical treatment for an extended period. NTZ was administered at a dose of 500 mg every 12 h for 3–24 months. In two out of five cases, the number of echinococcal cysts in the muscle tissue decreased, and in another case, it decreased in soft tissues and bones [29].

ANTIBACTERIAL ACTIVITY

NTZ can interfere with numerous metabolic pathways of bacterial cells, which consequently affects their viability and virulence. In *Escherichia coli*, it inhibits pyruvate dehydrogenase, which results in the disruption of energy metabolism [30]. It also disrupts biofilm formation and hemagglutination by enteroaggregative strains by blocking the assembly of AafA fimbriae [31]. Furthermore, this drug disrupts the membrane potential and acid–base equilibrium of *Mycobacterium tuberculosis* [32], inhibits the chaperone/usher pathway in Gram-negative bacteria, and disrupts the formation of fimbriae that promote colonization [13, 33]. According to M.A. Bailey et al. [34], NTZ is an effective treatment against *Mycobacterium leprae*. Administration of NTZ at a dose of 25 mg/kg through a probe to mice infected with *M. leprae* resulted in antimycobacterial activity equivalent to that of rifampicin at a dose of 10 mg/kg [34]. Furthermore, NTZ exhibited superior efficacy in improving clinical parameters and psychological state in patients with hepatic encephalopathy compared with rifaximin, a broad-spectrum antibacterial drug [35].

The efficacy of NTZ against *C. difficile* has been investigated extensively. A clinical trial demonstrated that NTZ was as effective as metronidazole in the treatment of cryptosporidiosis (Table 3). Furthermore, a study revealed activity of NTZ against metronidazole-resistant *C. difficile* strains [37].

Data confirm the efficacy of NTZs against *Helicobacter pylori*. In 2006, *Antimicrobial Agents and Chemotherapy* published a study on NTZ activity against *H. pylori* [38]. The authors concluded that NTZ is a noncompetitive inhibitor of pyruvate, i.e., ferredoxin/flavodoxinoxidoreductase, which is one of the most important enzymes

Table 3. Randomized double-blind trial comparing nitazoxanide and metronidazole in the treatment of patients hospitalized for colitis caused by *C. difficile* (USA, 2006)

Таблица 3. Рандомизированное двойное слепое исследование для сравнения нитазоксанида и метронидазола при лечении госпитализированных пациентов с колитом, вызванным *C. difficile* (США, 2006 г.)

Indicators	Metronidazole (250 mg every 6 h for 10 days)	Nitazoxanide (500 mg every 12 h for 7 days)	Nitazoxanide (500 mg every 12 h for 10 days)
Clinical response after 7 days of therapy	82.40%	90%	88.9%
Sustained clinical response after 31 days of therapy	57.60%	65.80%	74.3%
Efficacy of nitazoxanide compared with metronidazole	Effectiveness is comparable (95% CI 0.87–1.69; $p = 0.26$)		

involved in energy metabolism in *H. pylori* and other anaerobic bacteria. Owing to the targeting of NTZ on the activated cofactor of the enzymatic reaction rather than on its substrate, this drug can avoid drug resistance formation.

Subsequently, clinical trials were conducted in patients with a positive test for *H. pylori*. In 2016, a 2-week study of a combination of NTZ (500 mg daily), levofloxacin (500 mg daily), omeprazole (40 mg twice daily), and doxycycline (100 mg twice daily) was conducted at the outpatient department of Tanta University Hospital. The study included 100 patients who had previously received standard triple therapy, which included the use of levofloxacin (at a dose of 500 mg daily) in conjunction with proton pump inhibitors and amoxicillin (1 g twice daily). This treatment regimen had not yielded any positive results. Eradication was confirmed by *H. pylori* antigen in feces 6 weeks after the treatment. In total, 94 (94%) patients completed the study with excellent treatment compliance. Only 1 (1%) patient discontinued the treatment because of intolerable side effects, and 5 (5%) patients did not demonstrate good treatment compliance. Nevertheless, 83 patients had successful eradication of *H. pylori* with overall eradication rates of 83%. Side effects were reported in 21% of the patients, which included abdominal pain (6%), nausea (9%), constipation (12%), headache (2%), and dizziness (1%) [39].

In 2022, the *European Review for Medical and Pharmacological Sciences* published the results of a clinical trial investigating the efficacy of a combination of NTZ, a proton pump inhibitor, and clarithromycin in pediatric patients. The study enrolled 100 participants, which were divided into group 1 that received triple therapy based on NTZ (NTZ, proton pump inhibitor, and clarithromycin) for 14 days and group 2 that received standard treatment (metronidazole, omeprazole, and clarithromycin) for 14 days. A total of 92% of patients in the NTZ group and 84% in the metronidazole group recovered from the infection, with no statistically significant difference. The NTZ group exhibited a 54% lower risk of developing a resistant infection (odds ratio, 0.5, 95% CI 0.161–1.555) than the metronidazole group. In that study, NTZ-based therapy resulted in higher eradication rates than standard treatment. However, the difference was not statistically significant in this patient group [40].

ANTIVIRAL ACTIVITY

The initial documentation of the antiviral activity of NTZ emerged in 2006, when preliminary data confirmed its efficacy against rotavirus diarrhea in children [41]. In the same year, a double-blind placebo-controlled study of NTZ was conducted on 50 adult patients diagnosed with viral gastroenteritis caused by norovirus, rotavirus, or adenovirus. The results demonstrated a significant reduction in the disease course (rotavirus subgroup, $p = 0.0055$; norovirus subgroup, $p = 0.0295$) and the absence of undesirable effects from NTZ [42]. In subsequent years, NTZ trials against specific pathogens of viral gastroenteritis were conducted. Thus, in 2009, a blinded single randomized clinical trial demonstrated its efficacy in combination with probiotics compared with a placebo in children aged 28 days to 24 months diagnosed with rotavirus infection. The duration of hospitalization ($p = 0.017$) and median duration of diarrhea ($p = 0.009$) were evaluated [43]. NTZ also has a significant advantage in controlling norovirus in immunocompromised patients because of its ability to inhibit viral replication and act synergistically with ribavirin, thereby activating the cellular antiviral response [44]. Two clinical cases have been documented in which norovirus gastroenteritis was successfully treated with NTZ in organ transplant recipients receiving immunosuppressants, without a reduction in their dose [45, 46]. Furthermore, J. Morris et al. [47] reported the successful treatment of norovirus infection in 14 hematopoietic stem cell recipients undergoing chemotherapy and/or immunotherapy, with an average time to diarrhea resolution of 2–4 days. Preliminary data also indicate that NTZ may be effective in the treatment of diarrhea caused by adenovirus and astrovirus [48, 49].

NTZ garnered the attention of hepatologists in a study conducted in 2008, wherein it demonstrated efficacy against viral hepatitis B (VHB) and C (VHC) in cell cultures. Despite the lack of knowledge regarding its pharmacodynamics, *in vitro* studies have indicated that NTZ and its active metabolite tizaxonide exhibited selective inhibition of intracellular replication of VHB and VHC and extracellular virus production by cells. Several other thiazolides were found to be effective inhibitors of VHB replication in this assay system. Combinations of NTZs with either of two drugs licensed for anti-VHB therapy, such as lamivudine and adefovir, demonstrated synergistic interactions when used on VHB-infected cell cultures, and with recombinant interferon alpha-2b against VHC [50].

In 2009, the authors of the article "Potential for hepatitis C virus resistance to nitazoxanide or tizoxanide" concluded from *in vitro* experiments that NTZ and tizoxanide do not induce acquired resistance in VHC. The authors corroborated previous suggestions that NTZ and tizoxanide inhibit VHC replication through a cell-mediated mechanism that differs from that of classical virus-specific drugs but complements that of interferon alpha. They concluded that this class has the potential to be used for the treatment of chronic hepatitis C; however, further clinical studies are required [51].

The search for the mechanism of antiviral activity of NTZ and its efficacy against viral hepatitis continued. In 2014, O. Ashiru et al. [52] revealed that NTZ can lead to

endoplasmic reticulum (EPR) stress and the depletion of calcium ions accumulated in it and their release into the cytoplasm. Accordingly, the authors concluded that this process leads to the following consequences:

1. Increased cytoplasmic calcium levels promote the activation of protein kinase R, which plays an important role in the antiviral immune response by inducing inflammation.

2. Protein kinase R phosphorylates the translation factor eIF2α, which inactivates it. This results in the suppression of the synthesis of numerous cell proteins, including cell cycle activator proteins.

3. eIF2α blockage, in conjunction with the depletion of calcium stores within the EPR, may impair the proper folding and transport of proteins that are translated at the EPR membrane. This may inhibit the assembly of surface viral proteins, thereby reducing the viral load.

Apoptosis induction in response to EPR stress is thus suppressed by various mechanisms, including the induction of mitophagy, reduction of intracellular reactive oxygen species (ROS) concentration, and activation of cell signaling pathways that promote cell survival [52].

In 2018, *Cellular and Molecular Gastroenterology and Hepatology* published an article that provides the most comprehensive description of the recently discovered antiviral mechanisms of NTZ against VHB. These mechanisms include its inhibition of the interaction between HBx protein and DSB-1. A recent study demonstrated that the HBx protein causes the degradation of the Smc5/6 complex, which impairs the repair of homologous recombination of double-stranded DNA breaks and subsequent cellular transformation [53]. The HBx protein stabilizes viral DNA located in the nucleus of the host cell, which affects mainly virus replication, translation, and transcription of the viral genome [54]. K. Sekiba et al. [55] tested 817 candidate drugs for their potential to control VHB. Five candidate drugs were identified as having the most promising results, namely, toremifene, loperamide, pimozide, vinblastine, and NTZ. Some compounds did not show significant effects on different cell lines, whereas NTZ demonstrated the most consistent and pronounced inhibitory function among these compounds in HEK293T and HepG2 cells. Further experiments demonstrated that NTZ successfully inhibited the interaction between HBx and DSB-1, resulting in the restoration of Smc5/6 chromosome structural maintenance protein levels and suppression of viral transcription. The use of NTZ led to a significant reduction in the replication and synthesis of viral mRNA. These findings were corroborated by experiments conducted on a natural infection model, namely, a human hepatocyte cell line, which demonstrated that NTZ can inhibit virus replication at the early stages of reproduction [55].

Two pivotal studies of phase 2 clinical trials of NTZs against hepatitis C are worthy of particular attention. These studies are presented in the review article "Treatment of chronic viral hepatitis with nitazoxanide and second generation thiazolides," published in the *World Journal of Gastroenterology* in 2009. The authors reported that NTZ monotherapy resulted in a sustained antiviral response in 17% of the patients studied. A comparison of the standard treatment regimen and combination therapy with NTZ in combination with peginterferon alpha-2a (double combination) and NTZ in combination with peginterferon alpha-2a and ribavirin (triple combination) revealed a 29% difference in the rate of sustained viral response 24 weeks after treatment (Table 4) [56].

Nevertheless, in 2013, an independent randomized trial confirmed the efficacy of NTZ in the treatment of VHC. Patients with genotype 4 VHC who had not previously received treatment were enrolled in the study. Group 1 received weekly subcutaneous pegylated interferon at a dose of 160 mcg in addition to ribavirin in a weight-dependent manner (1200 and 1000 mg for weight ≥75 and <75 kg, respectively) for 48 weeks. Group 2 received NTZ monotherapy (500 mg twice daily) for 4 weeks, followed by triple therapy including NTZ, pegylated interferon, and ribavirin for a further 48 weeks. The authors concluded that the addition of NTZ to pegylated interferon and ribavirin did not improve the virologic or biochemical response rates in patients with chronic HCV genotype 4 [57].

Regarding VHB, in 2008, *The American Journal of Gastroenterology* published a report of two successful cases of NTZ monotherapy and its combination with adefovir. Patient 1 had VHB DNA and HBeAg before therapy. He was treated with NTZ at a dose of 500 mg twice daily. After 5 months of treatment, the patient discontinued therapy for 3 months because of high alanine aminotransferase levels. He then resumed treatment with a dose of

Table 4. Dependence of the formation of a stable viral response on the type of therapy for viral hepatitis C genotype 4 according to Ref. [56]

Таблица 4. Зависимость формирования устойчивого вирусного ответа от вида терапии при вирусном гепатите С генотипа 4 по данным работы [56]

Type of therapy	Development of a sustained viral response	*p*
Standard therapy (peginterferon alpha-2a + ribavirin)	50%	
Combination therapy (nitazoxanide + peginterferon alpha-2a)	61%	0.023
Combination therapy (nitazoxanide + peginterferon alpha-2a + ribavirin)	79%	

DOI: https://doi.org/10.17816/RCF624703

500 mg/day for 24 months. Patient 2 was HBeAg-positive before NTZ and adefovir therapy, and VHB DNA was also detected. He received adefovir at a dose of 10 mg/day for 2 years, in conjunction with 500 mg of NTZ twice daily (Table 6) [58].

In the second trial, published in 2019 in *Hepatology Communications*, the study enrolled nine men aged at least 17 years with chronic hepatitis B without cirrhosis with varying levels of detectable viral antigens. The drug was well tolerated with rare mild-to-moderate side effects, mostly gastrointestinal effects, including diarrhea and epigastric pain. These side effects were transient and resolved during treatment. No adverse events required treatment discontinuation. VHB DNA became undetectable (<38 IU/mL) in the serum of 8 of 9 (89%) patients after 4–20 weeks of NTZ therapy. The two patients who were positive for HBeAg tested negative after 4 and 16 weeks of treatment. HBsAg-negative results were observed in 3 of 9 (33%) patients, with two of these patients demonstrating a response after 8 weeks and one after 48 weeks of treatment (Table 7). The patient with delayed responses (20 weeks with undetectable VHB DNA, 16 weeks with an HBeAg-negative result, and 48 weeks with an HBsAg-negative result) received NTZ at a dose of 500 mg once daily [59].

The antiviral activity of NTZ was also demonstrated in an *in vitro* study against Ebola virus. L.D. Jasenosky et al. [60] validated previous hypotheses that NTZ enhances the innate antiviral cellular immune response. Consequently, NTZ was found to inhibit viral replication by enhancing the activity of retinoic acid-inducible gene 1 (*RIG-1*), which induces interferon (IFN)-1 family proteins. Furthermore, NTZ increased the overexpression of MAVS, a mitochondrial antiviral signaling protein that induces IFN-β expression through the activation of NF-κB and IRF3, thereby enhancing antiviral immunity [60–62].

NTZs have been tested against various airborne infections, including influenza viruses, paramyxoviruses, and rubella virus. D. Tilmanis et al. [63] demonstrated that NTZ exhibited high activity against 210 influenza viruses of type/subtype A(H1N1)pdm09, A(H3N2), B(Victoria lineage), and B(Yamagata lineage), including viruses resistant to neuraminidase inhibitors. These data are corroborated by the results of a double-blind, randomized, placebo-controlled trial involving 650 individuals with acute, uncomplicated influenza [64]. S. Piacentini et al. [65] reported the efficacy of NTZ against Sendai virus, a member of the paramyxovirus family, in cell cultures. The results demonstrated that NTZ significantly suppressed virus replication by inhibiting the synthesis and functioning of F-protein, an important pathogenicity factor for this virus, and reduced its cytopathic effect. The efficacy of NTZ against the rubella virus was demonstrated in an *in vitro* study that unveiled its dose-dependent inhibitory effect on this virus, regardless of the strain, and complete blocking of replication at a dose of 10 μg/mL [66].

A significant proportion of patients enrolled in clinical trials of NTZ exhibited an immunodeficient state, including those with HIV infection. One of the mechanisms of action of this drug is to enhance the innate antiviral response; accordingly, recent studies have demonstrated that it may be effective against HIV because of its

Table 5. Dependence of the formation of a stable viral response on the type of therapy for viral hepatitis C genotype 4 according to Ref. [57]

Таблица 5. Зависимость формирования устойчивого вирусного ответа от вида терапии при вирусном гепатите С генотипа 4 по данным работы [57]

Type of therapy	Development of a sustained viral response	*p*
Peginterferon alpha-2a + ribavirin (48 weeks)	48%	0.84
Nitazoxanide for 24 weeks, then nitazoxanide + peginterferon alpha-2a + ribavirin (48 weeks)	50%	

Table 6. Results of HCV treatment with NTZ and the combination of NTZ + adefovir

Таблица 6. Результаты лечения вирусном гепатите С (ВГВ) НТЗ и комбинацией НТЗ + адефовир

Patient	VHB DNA	HBeAg	HBsAg	HBsAt
No. 1	Negative	Negative	Negative	Negative
No. 2	Negative	Negative	Negative	Positive

Table 7. Activity of nitazoxanide in the treatment of nine patients with viral hepatitis B with different levels of detectable viral particles

Таблица 7. Исследование активности нитазоксанида при лечении 9 пациентов с вирусным гепатитом В (ВГВ) с различным уровнем определяемых вирусных частиц

Viral antigen detected in the patients	VHB DNA	HBeAg	HBsAg
Before therapy	100% (9 из 9)	22% (2 из 9)	100% (9 из 9)
After therapy	11% (1 из 9)	0 (0 из 9)	77% (7 из 9)

anti-inflammatory effect on certain stages of the HIV life cycle. This occurs through a synergistic interaction with cortisol and reverse transcriptase inhibitors [67] and a direct effect on proinflammatory cytokines. Thus, NTZ has a robust immunomodulatory effect, suppressing the production of proinflammatory mediators, including tumor necrosis factor-α, interleukins (ILs)-2, IL-4, IL-5, IL-6, IL-8, and IL-10 through various mechanisms [68, 69].

A summary of data indicates that NTZ is a broad-spectrum antiviral drug that enhances the innate antiviral immune response, suppresses inflammation, and affects key stages of the life cycle of some viruses by inhibiting the synthesis and functioning of viral proteins.

ANTITUMOR ACTIVITY

In 2013, N. Di Santo and J. Ehrisman proposed the antitumor activity of NTZ in ovarian cancer [70]. The authors posited that in ovarian tumor cells, the activity of protein disulfide isomerase (PDI) was increased, which was involved in the EPR stress response [71] and contributed to the survival of cancer cells. During EPR stress, an unfolded protein response is initiated to maintain the balance of protein folding within the EPR [72]. If this response is not initiated or the amount of unfolded proteins is excessive, EPR stress will lead to programmed cell death by apoptosis [73]. This mechanism could be employed in the treatment of tumor diseases. P.E. Lovat et al. [74] demonstrated that the antibiotic bacitracin induces the death of melanoma cells due to EPR stress. The capacity of this drug to inhibit PDI activity affects melanoma cells [75]. However, this drug has pronounced nephrotoxicity, which limits its use. In 2007, NTZ was found to inhibit PDI and induce apoptosis through EPR stress [76]. In contrast to bacitracin, NTZ has no pronounced side effects.

In addition to PDI, IL-6 is highly expressed in type 2 ovarian cancer cells [77]. IL-6, a proinflammatory cytokine, is involved in various inflammatory and autoimmune diseases, including cancer. In ovarian cancer, IL-6 increases tumor cell survival and enhances chemotherapy resistance through JAK/STAT signaling [78]. In 2012, a study demonstrated that NTZ directly suppressed IL-6 production *in vitro* and *in vivo* in laboratory mice [79], suggesting NTZ as a potential drug for the treatment of ovarian cancer.

In 2021, *Biochemical Pharmacology* published a study of NTZ activity on tumor cells in bladder cancer [80]. The authors elucidated that NTZ, by damaging mitochondria via PINK1-derived phospho-ubiquitinin and autophagy receptor-mediated pathway, can initiate mitophagy, which is a selective autophagy and leads to the selective removal of damaged or excess mitochondria [81]. Nevertheless, NTZ impedes the flux of mitophagy at the late stages by inhibiting lysosomal degradation activity. ROS produced by mitochondria are pivotal in this process. Therefore, the use of N-acetylcysteine, an antioxidant and cytoprotector [82], impeded PINK1-dependent initiation of mitophagy and alleviated lysosomal dysfunction. The concurrent use of nitazoxanide and chloroquine, a drug used in treating malaria and can inhibit autophagy [83], facilitated NTZ-induced apoptosis of bladder tumor cells. The study was conducted on 2D and 3D cell cultures that mimicked the *in vivo* situation. A significant reduction of orthotopic bladder tumors without significant systemic toxicity was found. The authors concluded that the use of NTZ involving AFC-mediated modulation of mitophagy at different stages is a potential therapeutic technique for bladder cancer.

In 2021, *Cancer Gene Therapy* published a study demonstrating the antitumor activity of NTZ in colorectal cancer. The farnesoid X receptor, which inhibits the production of bile acids, which can induce the development of colorectal cancer [84], acts as a colorectal tumor suppressor. Nevertheless, the high levels of β-catenin in tumor cells significantly diminish the antitumor activity of farnesoid X and obeticholic acid, which is its agonist. The antitumor activity of NTZ is manifested by the inhibition of β-catenin expression caused by the stabilization of PAD2, which is responsible for β-catenin citrulation and turnover in tumor cells [85]. Thus, the combination of obetichoic acid and NTZ may be a potential treatment for colorectal cancer [86].

A study of NTZ activity on the Wnt/β-catenin signaling pathway, which is involved in tumor cell proliferation and multidrug resistance formation, was published in 2022. Multidrug resistance is a significant challenge in the treatment of tumor diseases because it is formed simultaneously to a large group of drugs belonging to different classes [87]. *ABCB1* overexpression plays a pivotal role in the development of drug resistance, which results in the production of P-glycoprotein, a transmembrane pump that facilitates the elimination of numerous drugs from cells [88]. C-Myc and cyclin D1 were identified as proto-oncogenes downstream of the Wnt/β-catenin and MAPK pathways. The MAPK pathway regulates cell proliferation, differentiation, motility, and survival [89]. LS174T cell lines exposed to NTZ resulted in increased cell sensitivity to oxaliplatin, which is used as a first-line drug in the treatment of colorectal cancer. NTZ suppressed the Wnt/β-catenin signaling pathway by decreasing *ABCB1* activity and inhibiting c-Myc and cyclin D1 [90].

A study published in *Biological Chemistry* in 2022 investigated the effect of NTZ on human osteosarcoma (OS) cells *in vitro* and *in vivo*. The *in vitro* results demonstrated that NTZ inhibited cell proliferation, migration, and invasion, stopped the cell cycle in the G1 phase, and induced OS cell apoptosis. NTZ suppressed the activity of the AKT/mTOR signaling pathways, whose functions include the activation of cell growth, proliferation,

DOI: https://doi.org/10.17816/RCF624703

and angiogenesis, and Wnt/β-catenin signaling in OS cells. The results of the 143B orthotopic OS cell implantation model further confirmed that NTZ inhibited OS cell growth and lung metastasis *in vivo*. Notably, NTZ did not cause apparent damage to normal cells and tissues [92].

In 2022, a study of NTZ as a radiosensitizing drug was published [93]. In that study, NTZ selectively and synergistically sensitized tumor cells grown as spheroids to radiation. Furthermore, NTZ similarly inhibited tumor growth of HCT116 GFP xenograft cells in mice. NTZ was also found to selectively affect resting glucose-deprived tumor cells and increase their sensitivity to radiation *in vitro*. Consequently, the authors concluded that NTZ can be employed as a radiosensitizer.

Z. Lü et al. [94] demonstrated the effect of NTZ on 20S proteosomes [94], which are responsible for the degradation of cellular proteins [95]. The inhibition of all proteosome subunits by NTZ results in EPR stress, triggers the unfolded protein reaction, and induces autophagy at early stages, ultimately leading to cancer cell death.

A.M. Ghaleb et al. investigated the effect of NTZ on metastasis to bones in prostate cancer [96]. They concluded that NTZ demonstrated a significant inhibitory effect on bone metastases induced by the transcription factor KLF5, which stimulates cell proliferation. NTZ also inhibited osteoclast differentiation, a cellular process responsible for KLF5-induced bone metastasis. NTZ demonstrated the capacity to attenuate KLF5 function, with the regulation of 114 genes exhibiting a negative effect and 127 exhibiting a positive effect. In patients with prostate cancer, alterations in the expression of specific genes have been linked to poorer overall survival outcomes. One such alteration is the activation of *MYBL2*, which encodes a protein involved in cell cycle progression [97] and is involved in bone metastasis in prostate cancer. KLF5-K369Q binds to the MYBL2 promoter, activating its transcription. Further analysis demonstrated that NTZ bound to the KLF5 protein, thereby inhibiting the binding of KLF5-K369Q to the MYBL2 promoter [98].

The information obtained is the result of laboratory studies. Thus far, no clinical trials related to the use of NTZ in different types of tumors have been conducted.

CONCLUSIONS

In summary, the broad-spectrum thiazolid series drug NTZ has antibacterial, antiprotozoal, anthelminthic, antiviral, and antitumor activities. This is achieved through its pharmacological properties, namely, regulation of the cell cycle, apoptosis, proliferation, and migration; activation of links of innate immunity; influence on the synthesis and activation of cell proteins, some of which are links of cell signaling pathways; binding to proteins of viruses, bacteria, protozoa, and helminths with disruption of their vital activity; and immunomodeling action by regulating the activity of pro- and anti-inflammatory cytokines. The article presents a comprehensive overview of the current knowledge of the pharmacodynamics of NTZ, along with the findings of its preclinical and clinical trials. It also considers potential future developments. The results are of interest and may inform decisions regarding the need for preclinical and clinical trials of NTZ in these areas in Russia.

ADDITIONAL INFORMATION

Authors' contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study. The contribution of each author: A.A. Saveleva, Z.G. Tadtaeva, E.S. Astudin, A.S. Krivoshein, A.A. Akimov, N.A. Kuritsina — manuscript drafting, writing and pilot data analyses; V.V. Rusanovsky, Z.G. Tadtaeva — paper reconceptualization and general concept discussion.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

REFERENCES

1. Patent US 3950351. 1976 Apr 13. Rossignol JF, Cavier R. *New derivatives of 2-benzamido-5-nitro thiazoles*. Phavic Sprl, assignee.

2. Smart T. NTZ trials for cryptosporidiosis. *GMHC Treat Issues*. 1995;9(9):14.

3. Rossignol JF, Maisonneuve H. Nitazoxanide in the treatment of *Taenia saginata* and Hymenolepis nana infections. *Am J Trop Med Hyg*. 1984;33(3):511–512. doi: 10.4269/ajtmh.1984.33.511

4. Roehr B. Another failed promise? NTZ gets the nix. *J Int Assoc Physicians AIDS Care*. 1998;4(8):26–29.

5. Diaz E, Mondragon J, Ramirez E, Bernal R. Epidemiology and control of intestinal parasites with nitazoxanide in children in Mexico. *Am J Trop Med Hyg*. 2003;68(4):384–385.

6. Lateef M, Zargar SA, Khan AR, et al. Successful treatment of niclosamide- and praziquantel-resistant beef tapeworm infection with nitazoxanide. *Int J Infect Dis*. 2008;12(1):80–82. doi: 10.1016/j.ijid.2007.04.017

7. Rafiullah F, Kanwal S, Majeed UM, et al. Successful use of nitazoxanide in the treatment of recurrent *Clostridium difficile* infection. *BMJ Case Rep*. 2011;2011:bcr0420114123. doi: 10.1136/bcr.04.2011.4123

8. Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance-the need for global solutions. *Lancet Infect Dis*. 2013;13(12):1057–1098. doi: 10.1016/S1473-3099(13)70318-9

9. Rodriguez-Morales AJ, Martinez-Pulgarin DF, Muñoz-Urbano M, et al. Bibliometric assessment of the global scientific production of nitazoxanide. *Cureus*. 2017;9(5): e1204. doi: 10.7759/cureus.1204

10. Hemphill A, Mueller J, Esposito M. Nitazoxanide, a broad-spectrum thiazolide anti-infective agent for the treatment of gastrointestinal infections. *Expert Opin Pharmacother*. 2006;7(7):953–964. doi: 10.1517/14656566.7.7.953
11. Di Santo N, Ehrisman J. A functional perspective of nitazoxanide as a potential anticancer drug. *Mutat Res*. 2014;768:16–21. doi: 10.1016/j.mrfmmm.2014.05.005
12. alinia.com [internet]. Alinia (nitazoxanide) [cited 10 oct. 2023]. Available from: https://www.alinia.com/healthcare-professionals/
13. Shakya A, Bhat HR, Ghosh SK. Update on nitazoxanide: a multifunctional chemotherapeutic agent. *Curr Drug Discov Technol*. 2018;15(3):201–213. doi: 10.2174/1570163814666170727130003
14. Cedillo-Rivera R, Chávez B, González-Robles A, et al. *In vitro* effect of nitazoxanide against *Entamoeba histolytica*, *Giardia intestinalis* and *Trichomonas vaginalis* trophozoites. *J Eukaryot Microbiol*. 2002;49(3):201–208. doi: 10.1111/j.1550-7408.2002.tb00523.x
15. Hashan MR, Elhusseiny KM, Huu-Hoai L, et al. Effect of nitazoxanide on diarrhea: A systematic review and network meta-analysis of randomized controlled trials. *Acta Trop*. 2020;210:105603. doi: 10.1016/j.actatropica.2020.105603
16. Moron-Soto M, Gutierrez L, Sumano H, et al. Efficacy of nitazoxanide to treat natural Giardia infections in dogs. *Parasit Vectors*. 2017;10(1):52. doi: 10.1186/s13071-017-1998-7
17. Bailey JM, Erramouspe J. Nitazoxanide treatment for giardiasis and cryptosporidiosis in children. *Ann Pharmacother*. 2004;38(4):634–640. doi: 10.1345/aph.1D451
18. Doumbo O, Rossignol JF, Pichard E, et al. Nitazoxanide in the treatment of cryptosporidial diarrhea and other intestinal parasitic infections associated with acquired immunodeficiency syndrome in tropical Africa. *Am J Trop Med Hyg*. 1997;56(6):637–639. doi: 10.4269/ajtmh.1997.56.637
19. Li J, Kuang H, Zhan X. Nitazoxanide in the treatment of intestinal parasitic infections in children: a systematic review and meta-analysis. *Indian J Pediatr*. 2020;87(1):17–25. doi: 10.1007/s12098-019-03098-w
20. Rossignol JF, Ayoub A, Ayers MS. Treatment of diarrhea caused by *Giardia intestinalis* and *Entamoeba histolytica* or *E. dispar*: a randomized, double-blind, placebo-controlled study of nitazoxanide. *J Infect Dis.* 2001;184(3):381–384. doi: 10.1086/322038
21. Rossignol JF, Kabil SM, El-Gohary Y, Younis AM. Nitazoxanide in the treatment of amoebiasis. *Trans R Soc Trop Med Hyg*. 2007;101(10):1025–1031. doi: 10.1016/j.trstmh.2007.04.001
22. Goel V, Jain A, Sharma G, et al. Evaluating the efficacy of nitazoxanide in uncomplicated amebic liver abscess. *Indian J Gastroenterol*. 2021;40(3):272–280. doi: 10.1007/s12664-020-01132-w
23. SmirnovLP, Borvinskaya EV, Sukhovskaya IV, Kochneva AA. Glutathione s-transferases in helminths. *Trudy KarNTs RAN*. 2015;(11):3–14. EDN: VBCYRT doi: 10.17076/eb213 (In Russ.)
24. Halloran DM. Database of glutamate-gated chloride (GluCl) subunits across 125 nematode species: patterns of gene accretion and sequence diversification. *G3 (Bethesda).* 2022;12(2):jkab438. doi: 10.1093/g3journal/jkab438
25. El-Saber Batiha G, Alqahtani A, Ilesanmi OB, et al. Avermectin derivatives, pharmacokinetics, therapeutic and toxic dosages, mechanism of action, and their biological effects. *Pharmaceuticals (Basel).* 2020;13(8):196. doi: 10.3390/ph13080196
26. Chero JC, Saito M, Bustos JA, et al. Hymenolepis nana infection: symptoms and response to nitazoxanide in field conditions. *Trans R Soc Trop Med Hyg*. 2007;101(2):203–205. doi: 10.1016/j.trstmh.2006.04.004
27. Hu Y, Ellis BL, Yiu YY, et al. An extensive comparison of the effect of anthelmintic classes on diverse nematodes. *PLoS One*. 2013;8(7):e70702. doi: 10.1371/journal.pone.0070702
28. Pyzocha N, Cuda A. Common intestinal parasites. *Amer Fam Physician*. 2023;108(5):487–493. PMID: 37983700.
29. Pérez-Molina JA, Díaz-Menéndez M, Gallego JI, et al. Evaluation of nitazoxanide for the treatment of disseminated cystic echinococcosis: report of five cases and literature review. *Am J Trop Med Hyg*. 2011;84(2):351–356. doi: 10.4269/ajtmh.2011.10-0513
30. Hoffman PS, Sisson G, Croxen MA, et al. Antiparasitic drug nitazoxanide inhibits the pyruvate oxidoreductases of *Helicobacter pylori*, selected anaerobic bacteria and parasites, and *Campylobacter jejuni*. *Antimicrob Agents Chemother*. 2007;51(3):868–876. doi: 10.1128/AAC.01159-06
31. Shamir ER, Warthan M, Brown SP, et al. Nitazoxanide inhibits biofilm production and hemagglutination by enteroaggregative *Escherichia coli* strains by blocking assembly of AafA fimbriae. *Antimicrob Agents Chemother*. 2010;54(4):1526–1533. doi: 10.1128/AAC.01279-09
32. de Carvalho LP, Darby CM, Rhee KY, Nathan C. Nitazoxanide disrupts membrane potential and intrabacterial PH homeostasis of mycobacterium tuberculosis. *ACS Med Chem Lett.* 2011;2(11):849–854. doi: 10.1021/ml200157f
33. Busch A, Waksman G. Chaperone-usher pathways: diversity and pilus assembly mechanism. *Philos Trans R Soc Lond B Biol Sci*. 2012;367(1592):1112–1122. doi: 10.1098/rstb.2011.0206
34. Bailey MA, Na H, Duthie MS, et al. Nitazoxanide is active against *Mycobacterium leprae*. *PLoS One*. 2017;12(8):e0184107. doi: 10.1371/journal.pone.0184107
35. Glal KAM, Abd-Elsalam SM, Mostafa TM. Nitazoxanide versus rifaximin in preventing the recurrence of hepatic encephalopathy: A randomized double-blind controlled trial. *J Hepatobiliary Pancreat Sci.* 2021;28(10):812–824. doi: 10.1002/jhbp.947
36. Musher DM, Logan N, Hamill RJ, et al. Nitazoxanide for the treatment of *Clostridium difficile colitis*. *Clin Infect Dis*. 2006;43(4):421–427. doi: 10.1086/506351
37. Musher DM, Logan N, Mehendiratta V, et al. Clostridium difficile colitis that fails conventional metronidazole therapy: response to nitazoxanide. *J Antimicrob Chemother*. 2007;59(4):705–710. doi: 10.1093/jac/dkl553
38. Lanata CF, Franco M. Nitazoxanide for rotavirus diarrhoea? *Lancet*. 2006;368(9530):100–101. doi: 10.1016/S0140-6736(06)68981-2
39. Guevara B, Cogdill AG. *Helicobacter pylori*: A review of current diagnostic and management strategies. *Dig Dis Sci*. 2020;65(7):1917–1931. doi: 10.1007/s10620-020-06193-7
40. Abd-Elsalam S, Kobtan A, El-Kalla F, et al. A 2-week Nitazoxanide-based quadruple treatment as a rescue therapy for *Helicobacter pylori* eradication: A single center experience. *Medicine (Baltimore).* 2016;95(24): e3879. doi: 10.1097/MD.0000000000003879
41. Shawky D, Salamah AM, Abd-Elsalam SM, et al. Nitazoxanide-based therapeutic regimen as a novel treatment for *Helicobacter pylori* infection in children and adolescents: a randomized trial. *Eur Rev Med Pharmacol Sci*. 2022;26(9):3132–3137. doi: 10.26355/eurrev_202205_28730

42. Rossignol JF, El-Gohary YM. Nitazoxanide in the treatment of viral gastroenteritis: a randomized double-blind placebo-controlled clinical trial. *Aliment Pharmacol Ther*. 2006;24(10):1423–1430. doi: 10.1111/j.1365-2036.2006.03128.x
43. Teran CG, Teran-Escalera CN, Villarroel P. Nitazoxanide vs. probiotics for the treatment of acute rotavirus diarrhea in children: a randomized, single-blind, controlled trial in Bolivian children. *Int J Infect Dis*. 2009;13(4):518–523. doi: 10.1016/j.ijid.2008.09.014
44. Dang W, Xu L, Ma B, et al. Nitazoxanide inhibits human norovirus replication and synergizes with ribavirin by activation of cellular antiviral response. *Antimicrob Agents Chemother*. 2018;62(11): e00707–e00718. doi: 10.1128/aac. 00707-18
45. Siddiq DM, Koo HL, Adachi JA, Viola GM. Norovirus gastroenteritis successfully treated with nitazoxanide. *J Infect*. 2011;63(5): 394–397. doi: 10.1016/j.jinf.2011.08.002
46. Haubrich K, Gantt S, Blydt-Hansen T. Successful treatment of chronic norovirus gastroenteritis with nitazoxanide in a pediatric kidney transplant recipient. *Pediatr Transplant.* 2018;22(4):e13186. doi: 10.1111/petr.13186
47. Morris J, Morris C. Nitazoxanide is effective therapy for norovirus gastroenteritis after chemotherapy and hematopoietic stem cell transplantation (HSCT). *Biol Blood Marrow Transplant*. 2015;21(2):S255–S256. doi: 10.1016/j.bbmt.2014.11.405
48. Hargest V, Sharp B, Livingston B, et al. Astrovirus replication is inhibited by nitazoxanide *in vitro* and *in vivo*. *J Virol*. 2020;94(5): e01706–e0119. doi: 10.1128/JVI.01706-19
49. Esquer Garrigos Z, Barth D, Hamdi AM, et al. Nitazoxanide is a therapeutic option for adenovirus-related enteritis in immunocompromised adults. *Antimicrob Agents Chemother*. 2018;62(12): e01937–e01118. doi: 10.1128/AAC.01937-18
50. Rossignol JF. Thiazolides: a new class of antiviral drugs. *Expert Opin Drug Metab Toxicol*. 2009;5(6):667–674. doi: 10.1517/17425250902988487
51. Korba BE, Elazar M, Lui P, et al. Potential for hepatitis C virus resistance to nitazoxanide or tizoxanide. *Antimicrob Agents Chemother*. 2008;52(11):4069–4071. doi: 10.1128/AAC.00078-08
52. Ashiru O, Howe JD, Butters TD. Nitazoxanide, an antiviral thiazolide, depletes ATP-sensitive intracellular Ca(2+) stores. *Virology*. 2014;462–463:135–148. doi: 10.1016/j.virol.2014.05.015
53. Sekiba K, Otsuka M, Funato K, et al. HBx-induced degradation of Smc5/6 complex impairs homologous recombination-mediated repair of damaged DNA. *J Hepatol.* 2022;76(1):53–62. doi: 10.1016/j.jhep.2021.08.010
54. Schollmeier A, Glitscher M, Hildt E. Relevance of hbx for hepatitis B virus-associated pathogenesis. *Int J Mol Sci*. 2023;24(5):4964. doi: 10.3390/ijms24054964
55. Sekiba K, Otsuka M, Ohno M, et al. Inhibition of HBV transcription from CCCDNA with nitazoxanide by targeting the HBX-DDB1 interaction. *Cell Mol Gastroenterol Hepatol.* 2019;7(2):297–312. doi: 10.1016/j.jcmgh.2018.10.010
56. Nikolova K, Gluud C, Grevstad B, Jakobsen JC. Nitazoxanide for chronic hepatitis C. *Cochrane Database Syst Rev*. 2014;(4):CD009182. doi: 10.1002/14651858.CD009182.pub2
57. Shehab HM, Elbaz TM, Deraz DM. Nitazoxanide plus pegylated interferon and ribavirin in the treatment of genotype 4 chronic hepatitis C, a randomized controlled trial. *Liver Int*. 2014;34(2):259–265. doi: 10.1111/liv.12267
58. Kolozsi WZ, El-Gohary M, Keeffe MB, et al. Treatment of chronic hepatitis B (CHB) with nitazoxanide (Ntz) alone or Ntz plus adefovir (ADV) for two years with loss of hepatitis B e antigen (HBeAg) and hepatitis B surface antigen (HbsAg). *Am J Gastroenterol*. 2008;103: S150–S151. doi: 10.14309/00000434-200809001-00390
59. Rossignol JF, Bréchot C. A pilot clinical trial of nitazoxanide in the treatment of chronic hepatitis B. *Hepatol Commun*. 2019;3(6): 744–747. doi: 10.1002/hep4.1339
60. Jasenosky LD, Cadena C, Mire CE, et al. The FDA-approved oral drug nitazoxanide amplifies host antiviral responses and inhibits Ebola virus. *iScience*. 2019;19:1279–1290. doi: 10.1016/j.isci.2019.07.003
61. Matsumiya T, Stafforini DM. Function and regulation of retinoic acid-inducible gene-I. *Crit Rev Immunol*. 2010;30(6):489–513. doi: 10.1615/critrevimmunol.v30.i6.10
62. Zou PF, Tang JC, Li Y, et al. MAVS splicing variants associated with TRAF3 and TRAF6 in NF-κB and IRF3 signaling pathway in large yellow croaker *Larimichthys crocea*. *Dev Comp Immunol*. 2021;121:104076. doi: 10.1016/j.dci.2021.104076
63. Tilmanis D, van Baalen C, Oh DY, et al. The susceptibility of circulating human influenza viruses to tizoxanide, the active metabolite of nitazoxanide. *Antiviral Res*. 2017;147:142–148. doi: 10.1016/j.antiviral.2017.10.002
64. Haffizulla J, Hartman A, Hoppers M, et al.; US Nitazoxanide Influenza Clinical Study Group. Effect of nitazoxanide in adults and adolescents with acute uncomplicated influenza: a double-blind, randomised, placebo-controlled, phase 2b/3 trial. *Lancet Infect Dis*. 2014;14(7):609–618. doi: 10.1016/S1473-3099(14)70717-0
65. Piacentini S, La Frazia S, Riccio A, et al. Nitazoxanide inhibits paramyxovirus replication by targeting the Fusion protein folding: role of glycoprotein-specific thiol oxidoreductase ERp57. *Sci Rep*. 2018;8(1):10425. doi: 10.1038/s41598-018-28172-9
66. Perelygina L, Hautala T, Seppänen M, et al. Inhibition of rubella virus replication by the broad-spectrum drug nitazoxanide in cell culture and in a patient with a primary immune deficiency. *Antiviral Res*. 2017;147:58–66. doi: 10.1016/j.antiviral.2017.09.019
67. Gao G, Liu Y, Qu H, et al. Systematic identification of synergistic drug pairs targeting HIV. *Nat Biotechnol*. 2012;30(11):1125–1130. doi: 10.1038/nbt.2391
68. Clerici M, Trabattoni D, Pacei M, et al. The anti-infective nitazoxanide shows strong immumodulating effects (155.21). *J Immunol*. 2011;186(S1):155.21. doi: 10.4049/jimmunol.186.Supp.155.21
69. Purandare N, Gomez-Lopez N, Arenas-Hernandez M, et al. The MNRR1 activator nitazoxanide abrogates lipopolysaccharide-induced preterm birth in mice. *Placenta*. 2023;140:66–71. doi: 10.1016/j.placenta.2023.07.005
70. Di Santo N, Ehrisman J. Research perspective: potential role of nitazoxanide in ovarian cancer treatment. Old drug, new purpose? *Cancers (Basel).* 2013;5(3):1163–1176. doi: 10.3390/cancers5031163
71. Wang L, Wang X, Wang CC. Protein disulfide-isomerase, a folding catalyst and a redox-regulated chaperone. *Free Radic Biol Med*. 2015;83:305–313. doi: 10.1016/j.freeradbiomed.2015.02.007
72. Read A, Schröder M. The unfolded protein response: an overview. *Biology (Basel).* 2021;10(5):384. doi: 10.3390/biology10050384
73. Moenner M, Pluquet O, Bouchecareilh M, Chevet E. Integrated endoplasmic reticulum stress responses in cancer. *Cancer Res*. 2007;67(2):10631–10634. doi: 10.1158/0008-5472.CAN-07-1705
74. Lovat PE, Corazzari M, Armstrong JL, et al. Increasing melanoma cell death using inhibitors of protein disulfide isomerases to

abrogate survival responses to endoplasmic reticulum stress. *Cancer Res*. 2008;68(13):5363–5369. doi: 10.1158/0008-5472.CAN-08-0035
75. Dickerhof N, Kleffmann T, Jack R, McCormick S. Bacitracin inhibits the reductive activity of protein disulfide isomerase by disulfide bond formation with free cysteines in the substrate-binding domain. *FEBS J*. 2011;278(12):2034–2043. doi: 10.1111/j.1742-4658.2011.08119.x
76. Müller J, Naguleswaran A, Müller N, Hemphill A. Neospora caninum: Functional inhibition of protein disulfide isomerase by the broad-spectrum anti-parasitic drug nitazoxanide and other thiazolides. *Exp Parasitol*. 2008;118(1):80–88. doi: 10.1016/j.exppara.2007.06.008
77. Lane D, Matte I, Rancourt C, Piché A. Prognostic significance of IL-6 and IL-8 ascites levels in ovarian cancer patients. *BMC Cancer*. 2011;11:210. doi: 10.1186/1471-2407-11-210
78. Naugler WE, Karin M. The wolf in sheep' s clothing: The role of interleukin-6 in immunity, inflammation and cancer. *Trends Mol Med*. 2008;14(3):109–119. doi: 10.1016/j.molmed.2007.12.007
79. Hong SK, Kim HJ, Song CS, et al. Nitazoxanide suppresses IL-6 production in LPS-stimulated mouse macrophages and TG-injected mice. *Int Immunopharmacol*. 2012;13(1):23–27. doi: 10.1016/j.intimp.2012.03.002
80. Sun H, Ou T, Hu J, et al. Nitazoxanide impairs mitophagy flux through ROS-mediated mitophagy initiation and lysosomal dysfunction in bladder cancer. *Biochem Pharmacol*. 2021;190:114588. doi: 10.1016/j.bcp.2021.114588
81. Ding WX, Yin XM. Mitophagy: mechanisms, pathophysiological roles, and analysis. *Biol Chem*. 2012;393(7):547–564. doi: 10.1515/hsz-2012-0119
82. Ezeriņa D, Takano Y, Hanaoka K, et al. N-Acetyl cysteine functions as a fast-acting antioxidant by triggering intracellular H_2S and sulfane sulfur production. *Cell Chem Biol*. 2018;25(4):447–459.e4. doi: 10.1016/j.chembiol.2018.01.011
83. Mauthe M, Orhon I, Rocchi C, et al. Chloroquine inhibits autophagic flux by decreasing autophagosome-lysosome fusion. *Autophagy*. 2018;14(8):1435–1455. doi: 10.1080/15548627.2018.1474314
84. Nguyen TT, Ung TT, Kim NH, Jung YD. Role of bile acids in colon carcinogenesis. *World J Clin Cases*. 2018;6(13):577–588. doi: 10.12998/wjcc.v6.i13.577
85. NTZ Increases β-catenin Citrullination to Suppress WNT Signaling. *Cancer Discov*. 2018;8(1):OF19. doi: 10.1158/2159-8290.CD-RW2017-214
86. Yu J, Yang K, Zheng J, et al. Synergistic tumor inhibition of colon cancer cells by nitazoxanide and obeticholic acid, a farnesoid X receptor ligand. *Cancer Gene Ther*. 2021;28(6):590–601. doi: 10.1038/s41417-020-00239-8
87. Emran TB, Shahriar A, Mahmud AR, et al. Multidrug resistance in cancer: understanding molecular mechanisms, immunoprevention and therapeutic approaches. *Front Oncol*. 2022;12:891652. doi: 10.3389/fonc.2022.891652
88. Hodges LM, Markova SM, Chinn LW, et al. Very important pharmacogene summary: ABCB1 (MDR1, P-glycoprotein). *Pharmacogenet Genomics*. 2011;21(3):152–161. doi: 10.1097/FPC.0b013e3283385a1c
89. Cargnello M, Roux PP. Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases. *Microbiol Mol Biol Rev*. 2011;75(1):50–83. doi: 10.1128/MMBR.00031-10
90. Hemmati-Dinarvand M, Ahmadvand H, Seghatoleslam A. Nitazoxanide and cancer drug resistance: targeting Wnt/β-catenin signaling pathway. *Arch Med Res*. 2022;53(3):263–270. doi: 10.1016/j.arcmed.2021.12.001
91. Li H, Zeng J, Shen K. PI3K/AKT/mTOR signaling pathway as a therapeutic target for ovarian cancer. *Arch Gynecol Obstet*. 2014;290(6):1067–1078. doi: 10.1007/s00404-014-3377-3
92. Ye C, Wei M, Huang H, et al. Nitazoxanide inhibits osteosarcoma cells growth and metastasis by suppressing AKT/mTOR and Wnt/β-catenin signaling pathways. *Biol Chem*. 2022;403(10):929–943. doi: 10.1515/hsz-2022-0148
93. Karlsson H, Fryknäs M, Senkowski W, et al. Selective radiosensitization by nitazoxanide of quiescent clonogenic colon cancer tumour cells. *Oncol Lett*. 2022;23(4):123. doi: 10.3892/ol.2022.13243
94. Lü Z, Li X, Li K, et al. Nitazoxanide and related thiazolides induce cell death in cancer cells by targeting the 20S proteasome with novel binding modes. *Biochem Pharmacol*. 2022;197:114913. doi: 10.1016/j.bcp.2022.114913
95. Coux O, Tanaka K, Goldberg AL. Structure and functions of the 20S and 26S proteasomes. *Annu Rev Biochem*. 1996;65:801–847. doi: 10.1146/annurev.bi.65.070196.004101
96. Ghaleb AM, Nandan MO, Chanchevalap S, et al. Krüppel-like factors 4 and 5: the yin and yang regulators of cellular proliferation. *Cell Res*. 2005;15(2):92–96. doi: 10.1038/sj.cr.7290271
97. MYBL2 MYB proto-oncogene like 2 [*Homo sapiens* (human)] Gene ID: 4605, updated on 10-Oct-2023
98. Huang Q, Liu M, Zhang D, et al. Nitazoxanide inhibits acetylated KLF5-induced bone metastasis by modulating KLF5 function in prostate cancer. *BMC Med*. 2023;21(1):68. doi: 10.1186/s12916-023-02763-4

СПИСОК ЛИТЕРАТУРЫ

1. Patent US 3950351. 1976 Apr 13. Rossignol J.F., Cavier R. New derivatives of 2-benzamido-5-nitro thiazoles. Phavic Sprl, assignee.
2. Smart T. NTZ trials for cryptosporidiosis // GMHC Treat Issues. 1995. Vol. 9, N. 9. P. 14.
3. Rossignol J.F., Maisonneuve H. Nitazoxanide in the treatment of *Taenia saginata* and *Hymenolepis nana* infections // Am J Trop Med Hyg. 1984. Vol. 33, N. 3. P. 511–512. doi: 10.4269/ajtmh.1984.33.511
4. Roehr B. Another failed promise? NTZ gets the nix // J Int Assoc Physicians AIDS Care. 1998. Vol. 4, N. 8. P. 26–29.
5. Diaz E., Mondragon J., Ramirez E., Bernal R. Epidemiology and control of intestinal parasites with nitazoxanide in children in Mexico // Am J Trop Med Hyg. 2003. Vol. 68, N. 4. P. 384–385.
6. Lateef M., Zargar S.A., Khan A.R., et al. Successful treatment of niclosamide- and praziquantel-resistant beef tapeworm infection with nitazoxanide // Int J Infect Dis. 2008. Vol. 12, N. 1. P. 80–82. doi: 10.1016/j.ijid.2007.04.017
7. Rafiullah F., Kanwal S., Majeed U.M., et al. Successful use of nitazoxanide in the treatment of recurrent *Clostridium difficile* infection // BMJ Case Rep. 2011. Vol. 2011. P. bcr0420114123. doi: 10.1136/bcr.04.2011.4123
8. Laxminarayan R., Duse A., Wattal C., et al. Antibiotic resistance-the need for global solutions // Lancet Infect Dis. 2013. Vol. 13, N. 12. P. 1057–1098. doi: 10.1016/S1473-3099(13)70318-9

9. Rodriguez-Morales A.J., Martinez-Pulgarin D.F., Muñoz-Urbano M., et al. Bibliometric assessment of the global scientific production of nitazoxanide // Cureus. 2017. Vol. 9, N. 5. P. e1204. doi: 10.7759/cureus.1204
10. Hemphill A., Mueller J., Esposito M. Nitazoxanide, a broad-spectrum thiazolide anti-infective agent for the treatment of gastrointestinal infections // Expert Opin Pharmacother. 2006. Vol. 7, N. 7. P. 953–964. doi: 10.1517/14656566.7.7.953
11. Di Santo N., Ehrisman J. A functional perspective of nitazoxanide as a potential anticancer drug // Mutat Res. 2014. Vol. 768. P. 16–21. doi: 10.1016/j.mrfmmm.2014.05.005
12. alinia.com [интернет]. Alinia (nitazoxanide). Режим доступа: https://www.alinia.com/healthcare-professionals/ Дата обращения: 10.10.2023.
13. Shakya A., Bhat H.R., Ghosh S.K. Update on Nitazoxanide: a multifunctional chemotherapeutic agent // Curr Drug Discov Technol. 2018. Vol. 15, N. 3. P. 201–213. doi: 10.2174/1570163814666170727130003
14. Cedillo-Rivera R., Chávez B., González-Robles A., et al. *In vitro* effect of nitazoxanide against *Entamoeba histolytica*, *Giardia intestinalis* and *Trichomonas vaginalis* trophozoites // J Eukaryot Microbiol. 2002. Vol. 49, N. 3. P. 201–208. doi: 10.1111/j.1550-7408.2002.tb00523.x
15. Hashan M.R., Elhusseiny K.M., Huu-Hoai L., et al. Effect of nitazoxanide on diarrhea: A systematic review and network meta-analysis of randomized controlled trials // Acta Trop. 2020. Vol. 210. P. 105603. doi: 10.1016/j.actatropica.2020.105603
16. Moron-Soto M., Gutierrez L., Sumano H., et al. Efficacy of nitazoxanide to treat natural Giardia infections in dogs // Parasit Vectors. 2017. Vol. 10, N. 1. P. 52. doi: 10.1186/s13071-017-1998-7
17. Bailey J.M., Erramouspe J. Nitazoxanide treatment for giardiasis and cryptosporidiosis in children // Ann Pharmacother. 2004. Vol. 38, N. 4. P. 634–640. doi: 10.1345/aph.1D451
18. Doumbo O., Rossignol J.F., Pichard E., et al. Nitazoxanide in the treatment of cryptosporidial diarrhea and other intestinal parasitic infections associated with acquired immunodeficiency syndrome in tropical Africa // Am J Trop Med Hyg. 1997. Vol. 56, N. 6. P. 637–639. doi: 10.4269/ajtmh.1997.56.637
19. Li J., Kuang H., Zhan X. Nitazoxanide in the treatment of intestinal parasitic infections in children: a systematic review and meta-analysis // Indian J Pediatr. 2020. Vol. 87, N. 1. P. 17–25. doi: 10.1007/s12098-019-03098-w
20. Rossignol J.F., Ayoub A., Ayers M.S. Treatment of diarrhea caused by *Giardia intestinalis* and *Entamoeba histolytica* or *E. dispar*: a randomized, double-blind, placebo-controlled study of nitazoxanide // J Infect Dis. 2001. Vol. 184, N. 3. P. 381–384. doi: 10.1086/322038
21. Rossignol J.F., Kabil S.M., El-Gohary Y., Younis A.M. Nitazoxanide in the treatment of amoebiasis // Trans R Soc Trop Med Hyg. 2007. Vol. 101, N. 10. P. 1025–1031. doi: 10.1016/j.trstmh.2007.04.001
22. Goel V., Jain A., Sharma G., et al. Evaluating the efficacy of nitazoxanide in uncomplicated amebic liver abscess // Indian J Gastroenterol. 2021. Vol. 40, N. 3. P. 272–280. doi: 10.1007/s12664-020-01132-w
23. Смирнов Л.Л., Борвинская Е.В., Кочнева А.А., Суховская И.В. Глутатион-S-трансферазы у гельминтов // Труды КарНЦ РАН. 2015. № 11. С. 3–14. EDN: VBCYRT doi: 10.17076/eb213
24. Halloran D.M. Database of glutamate-gated chloride (GluCl) subunits across 125 nematode species: patterns of gene accretion and sequence diversification // G3 (Bethesda). 2022. Vol. 12, N. 2. P. jkab438. doi: 10.1093/g3journal/jkab438
25. El-Saber Batiha G., Alqahtani A., Ilesanmi O.B., et al. Avermectin derivatives, pharmacokinetics, therapeutic and toxic dosages, mechanism of action, and their biological effects // Pharmaceuticals (Basel). 2020. Vol. 13, N. 8. P. 196. doi: 10.3390/ph13080196
26. Chero J.C., Saito M., Bustos J.A., et al. Hymenolepis nana infection: symptoms and response to nitazoxanide in field conditions // Trans R Soc Trop Med Hyg. 2007. Vol. 101, N. 2. P. 203–205. doi: 10.1016/j.trstmh.2006.04.004
27. Hu Y., Ellis B.L., Yiu Y.Y., et al. An extensive comparison of the effect of anthelmintic classes on diverse nematodes // PLoS One. 2013. Vol. 8, N. 7. P. e70702. doi: 10.1371/journal.pone.0070702
28. Pyzocha N., Cuda A. Common intestinal parasites // Amer Fam Physician. 2023. Vol. 108, N. 5. P. 487–493. PMID: 37983700
29. Pérez-Molina J.A., Díaz-Menéndez M., Gallego J.I., et al. Evaluation of nitazoxanide for the treatment of disseminated cystic echinococcosis: report of five cases and literature review // Am J Trop Med Hyg. 2011. Vol. 84, N. 2. P. 351–356. doi: 10.4269/ajtmh.2011.10-0513
30. Hoffman P.S., Sisson G., Croxen M.A., et al. Antiparasitic drug nitazoxanide inhibits the pyruvate oxidoreductases of *Helicobacter pylori*, selected anaerobic bacteria and parasites, and *Campylobacter jejuni* // Antimicrob Agents Chemother. 2007. Vol. 51, N. 3. P. 868–876. doi: 10.1128/AAC.01159-06
31. Shamir E.R., Warthan M., Brown S.P., et al. Nitazoxanide inhibits biofilm production and hemagglutination by enteroaggregative *Escherichia coli* strains by blocking assembly of AafA fimbriae // Antimicrob Agents Chemother. 2010. Vol. 54, N. 4. P. 1526–1533. doi: 10.1128/AAC.01279-09
32. de Carvalho LP, Darby CM, Rhee KY, Nathan C. Nitazoxanide disrupts membrane potential and intrabacterial PH homeostasis of mycobacterium tuberculosis // ACS Med Chem Lett. 2011. Vol. 2, N. 11. P. 849–854. doi: 10.1021/ml200157f
33. Busch A., Waksman G. Chaperone-usher pathways: diversity and pilus assembly mechanism // Philos Trans R Soc Lond B Biol Sci. 2012. Vol. 367, N. 1592. P. 1112–1122. doi: 10.1098/rstb.2011.0206
34. Bailey M.A., Na H., Duthie M.S., et al. Nitazoxanide is active against *Mycobacterium leprae* // PLoS One. 2017. Vol. 12, N. 8. P. e0184107. doi: 10.1371/journal.pone.0184107
35. Glal K.A.M., Abd-Elsalam S.M., Mostafa T.M. Nitazoxanide versus rifaximin in preventing the recurrence of hepatic encephalopathy: A randomized double-blind controlled trial // J Hepatobiliary Pancreat Sci. 2021. Vol. 28, N. 10. P. 812–824. doi: 10.1002/jhbp.947
36. Musher D.M., Logan N., Hamill R.J., et al. Nitazoxanide for the treatment of *Clostridium difficile colitis* // Clin Infect Dis. 2006. Vol. 43, N. 4. P. 421–427. doi: 10.1086/506351
37. Musher D.M., Logan N., Mehendiratta V., et al. Clostridium difficile colitis that fails conventional metronidazole therapy: response to nitazoxanide // J Antimicrob Chemother. 2007. Vol. 59, N. 4. P. 705–710. doi: 10.1093/jac/dkl553
38. Lanata C.F., Franco M. Nitazoxanide for rotavirus diarrhoea? // Lancet. 2006. Vol. 368, N. 9530. P. 100–101. doi: 10.1016/S0140-6736(06)68981-2
39. Guevara B., Cogdill A.G. *Helicobacter pylori*: A review of current diagnostic and management strate-

gies // Dig Dis Sci. 2020. Vol. 65, N. 7. P. 1917–1931. doi: 10.1007/s10620-020-06193-7

40. Abd-Elsalam S., Kobtan A., El-Kalla F., et al. A 2-week Nitazoxanide-based quadruple treatment as a rescue therapy for *Helicobacter pylori* eradication: A single center experience // Medicine (Baltimore). 2016. Vol. 95, N. 24. P. e3879. doi: 10.1097/MD.0000000000003879

41. Shawky D., Salamah A.M., Abd-Elsalam S.M., et al. Nitazoxanide-based therapeutic regimen as a novel treatment for *Helicobacter pylori* infection in children and adolescents: a randomized trial // Eur Rev Med Pharmacol Sci. 2022. Vol. 26, N. 9. P. 3132–3137. doi: 10.26355/eurrev_202205_28730

42. Rossignol J.F., El-Gohary Y.M. Nitazoxanide in the treatment of viral gastroenteritis: a randomized double-blind placebo-controlled clinical trial // Aliment Pharmacol Ther. 2006. Vol. 24, N. 10. P. 1423–1430. doi: 10.1111/j.1365-2036.2006.03128.x

43. Teran C.G., Teran-Escalera C.N., Villarroel P. Nitazoxanide vs. probiotics for the treatment of acute rotavirus diarrhea in children: a randomized, single-blind, controlled trial in Bolivian children // Int J Infect Dis. 2009. Vol. 13, N. 4. P. 518–523. doi: 10.1016/j.ijid.2008.09.014

44. Dang W., Xu L., Ma B., et al. Nitazoxanide inhibits human norovirus replication and synergizes with ribavirin by activation of cellular antiviral response // Antimicrob Agents Chemother. 2018. Vol. 62, N. 11. P. e00707–e00718. doi: 10.1128/aac. 00707-18

45. Siddiq D.M., Koo H.L., Adachi J.A., Viola G.M. Norovirus gastroenteritis successfully treated with nitazoxanide // J Infect. 2011. Vol. 63, N. 5. P. 394–397. doi: 10.1016/j.jinf.2011.08.002

46. Haubrich K., Gantt S., Blydt-Hansen T. Successful treatment of chronic norovirus gastroenteritis with nitazoxanide in a pediatric kidney transplant recipient // Pediatr Transplant. 2018. Vol. 22, N. 4. P. e13186. doi: 10.1111/petr.13186

47. Morris J., Morris C. Nitazoxanide is effective therapy for norovirus gastroenteritis after chemotherapy and hematopoietic stem cell transplantation (HSCT) // Biol Blood Marrow Transplant. 2015. Vol. 21, N. 2. P. S255–S256. doi: 10.1016/j.bbmt.2014.11.405

48. Hargest V., Sharp B., Livingston B., et al. Astrovirus replication is inhibited by nitazoxanide *in vitro* and *in vivo* // J Virol. 2020. Vol. 94, N. 5. P. e01706–e0119. doi: 10.1128/JVI.01706-19

49. Esquer Garrigos Z., Barth D., Hamdi A.M., et al. Nitazoxanide is a therapeutic option for adenovirus-related enteritis in immunocompromised adults // Antimicrob Agents Chemother. 2018. Vol. 62, N. 12. P. e01937–e01118. doi: 10.1128/AAC.01937-18

50. Rossignol J.F. Thiazolides: a new class of antiviral drugs // Expert Opin Drug Metab Toxicol. 2009. Vol. 5, N. 6. P. 667–674. doi: 10.1517/17425250902988487

51. Korba B.E., Elazar M., Lui P., et al. Potential for hepatitis C virus resistance to nitazoxanide or tizoxanide // Antimicrob Agents Chemother. 2008. Vol. 52, N. 11. P. 4069–4071. doi: 10.1128/AAC.00078-08

52. Ashiru O., Howe J.D., Butters T.D. Nitazoxanide, an antiviral thiazolide, depletes ATP-sensitive intracellular Ca(2+) stores // Virology. 2014. Vol. 462–463. P. 135–148. doi: 10.1016/j.virol.2014.05.015

53. Sekiba K., Otsuka M., Funato K., et al. HBx-induced degradation of Smc5/6 complex impairs homologous recombination-mediated repair of damaged DNA // J Hepatol. 2022. Vol. 76, N. 1. P. 53–62. doi: 10.1016/j.jhep.2021.08.010

54. Schollmeier A., Glitscher M., Hildt E. Relevance of HBx for hepatitis B virus-associated pathogenesis // Int J Mol Sci. 2023. Vol. 24, N. 5. P. 4964. doi: 10.3390/ijms24054964

55. Sekiba K., Otsuka M., Ohno M., et al. Inhibition of HBV transcription from cccDNA With nitazoxanide by targeting the HBx-DDB1 interaction // Cell Mol Gastroenterol Hepatol. 2019. Vol. 7, N. 2. P. 297–312. doi: 10.1016/j.jcmgh.2018.10.010

56. Nikolova K., Gluud C., Grevstad B., Jakobsen J.C. Nitazoxanide for chronic hepatitis C // Cochrane Database Syst Rev. 2014. N. 4. P. CD009182. doi: 10.1002/14651858.CD009182.pub2

57. Shehab H.M., Elbaz T.M., Deraz D.M. Nitazoxanide plus pegylated interferon and ribavirin in the treatment of genotype 4 chronic hepatitis C, a randomized controlled trial // Liver Int. 2014. Vol. 34, N. 2. P. 259–265. doi: 10.1111/liv.12267

58. Kolozsi W.Z., El-Gohary M., Keeffe M.B., et al. Treatment of chronic hepatitis B (CHB) with nitazoxanide (Ntz) Alone or Ntz Plus Adefovir (ADV) for two years with loss of hepatitis B E antigen (HBeAg) and hepatitis B surface antigen (HbsAg) // Am J Gastroenterol. 2008. Vol. 103. P. S150–S151. doi: 10.14309/00000434-200809001-00390

59. Rossignol J.F., Bréchot C. A Pilot Clinical Trial of Nitazoxanide in the Treatment of Chronic Hepatitis B // Hepatol Commun. 2019. Vol. 3, N. 6. P. 744–747. doi: 10.1002/hep4.1339

60. Jasenosky L.D., Cadena C., Mire C.E., et al. The FDA-approved oral drug nitazoxanide amplifies host antiviral responses and inhibits ebola virus // iScience. 2019. Vol. 19. P. 1279–1290. doi: 10.1016/j.isci.2019.07.003

61. Matsumiya T., Stafforini D.M. Function and regulation of retinoic acid-inducible gene-I // Crit Rev Immunol. 2010. Vol. 30, N. 6. P. 489–513. doi: 10.1615/critrevimmunol.v30.i6.10

62. Zou P.F., Tang J.C., Li Y., et al. MAVS splicing variants associated with TRAF3 and TRAF6 in NF-κB and IRF3 signaling pathway in large yellow croaker *Larimichthys crocea* // Dev Comp Immunol. 2021. Vol. 121. P. 104076. doi: 10.1016/j.dci.2021.104076

63. Tilmanis D., van Baalen C., Oh D.Y., et al. The susceptibility of circulating human influenza viruses to tizoxanide, the active metabolite of nitazoxanide // Antiviral Res. 2017. Vol. 147. P. 142–148. doi: 10.1016/j.antiviral.2017.10.002

64. Haffizulla J., Hartman A., Hoppers M., et al.; US Nitazoxanide Influenza Clinical Study Group. Effect of nitazoxanide in adults and adolescents with acute uncomplicated influenza: a double-blind, randomised, placebo-controlled, phase 2b/3 trial // Lancet Infect Dis. 2014. Vol. 14, N. 7. P. 609–618. doi: 10.1016/S1473-3099(14)70717-0

65. Piacentini S., La Frazia S., Riccio A., et al. Nitazoxanide inhibits paramyxovirus replication by targeting the Fusion protein folding: role of glycoprotein-specific thiol oxidoreductase ERp57 // Sci Rep. 2018. Vol. 8, N. 1. P. 10425. doi: 10.1038/s41598-018-28172-9

66. Perelygina L., Hautala T., Seppänen M., et al. Inhibition of rubella virus replication by the broad-spectrum drug nitazoxanide in cell culture and in a patient with a primary immune deficiency // Antiviral Res. 2017. Vol. 147. P. 58–66. doi: 10.1016/j.antiviral.2017.09.019

67. Gao G., Liu Y., Qu H., et al. Systematic identification of synergistic drug pairs targeting HIV // Nat Biotechnol. 2012. Vol. 30, N. 11. P. 1125–1130. doi: 10.1038/nbt.2391

68. Clerici M., Trabattoni D., Pacei M., et al. The anti-infective Nitazoxanide shows strong immumodulating effects (155.21) // J Immunol. 2011. Vol. 186, N. S1. P. 155.21. doi: 10.4049/jimmunol.186.Supp.155.21

69. Purandare N., Gomez-Lopez N., Arenas-Hernandez M., et al. The MNRR1 activator nitazoxanide abrogates lipopolysaccharide-induced preterm birth in mice // Placenta. 2023. Vol. 140. P. 66–71. doi: 10.1016/j.placenta.2023.07.005

70. Di Santo N., Ehrisman J. Research perspective: potential role of nitazoxanide in ovarian cancer treatment. Old drug, new purpose? // Cancers (Basel). 2013. Vol. 5, N. 3. P. 1163–1176. doi: 10.3390/cancers5031163

71. Wang L., Wang X., Wang C.C. Protein disulfide-isomerase, a folding catalyst and a redox-regulated chaperone // Free Radic Biol Med. 2015. Vol. 83. P. 305–313. doi: 10.1016/j.freeradbiomed.2015.02.007

72. Read A., Schröder M. The unfolded protein response: an overview // Biology (Basel). 2021. Vol. 10, N. 5. P. 384. doi: 10.3390/biology10050384

73. Moenner M., Pluquet O., Bouchecareilh M., Chevet E. Integrated endoplasmic reticulum stress responses in cancer // Cancer Res. 2007. Vol. 67, N. 2. P. 10631–10634. doi: 10.1158/0008-5472.CAN-07-1705

74. Lovat P.E., Corazzari M., Armstrong J.L., et al. Increasing melanoma cell death using inhibitors of protein disulfide isomerases to abrogate survival responses to endoplasmic reticulum stress // Cancer Res. 2008. Vol. 68, N. 13. P. 5363–5369. doi: 10.1158/0008-5472.CAN-08-0035

75. Dickerhof N., Kleffmann T., Jack R., McCormick S. Bacitracin inhibits the reductive activity of protein disulfide isomerase by disulfide bond formation with free cysteines in the substrate-binding domain // FEBS J. 2011. Vol. 278, N. 12. P. 2034–2043. doi: 10.1111/j.1742-4658.2011.08119.x

76. Müller J., Naguleswaran A., Müller N., Hemphill A. *Neospora caninum*: Functional inhibition of protein disulfide isomerase by the broad-spectrum anti-parasitic drug nitazoxanide and other thiazolides // Exp Parasitol. 2008. Vol. 118, N. 1. P. 80–88. doi: 10.1016/j.exppara.2007.06.008

77. Lane D., Matte I., Rancourt C., Piché A. Prognostic significance of IL-6 and IL-8 ascites levels in ovarian cancer patients // BMC Cancer. 2011. Vol. 11. P. 210. doi: 10.1186/1471-2407-11-210

78. Naugler W.E., Karin M. The wolf in sheep&apos. Vol. s clothing: The role of interleukin-6 in immunity, inflammation and cancer // Trends Mol Med. 2008. Vol. 14, N. 3. P. 109–119. doi: 10.1016/j.molmed.2007.12.007

79. Hong S.K., Kim H.J., Song C.S., et al. Nitazoxanide suppresses IL-6 production in LPS-stimulated mouse macrophages and TG-injected mice // Int Immunopharmacol. 2012. Vol. 13, N. 1. P. 23–27. doi: 10.1016/j.intimp.2012.03.002

80. Sun H., Ou T., Hu J., et al. Nitazoxanide impairs mitophagy flux through ROS-mediated mitophagy initiation and lysosomal dysfunction in bladder cancer // Biochem Pharmacol. 2021. Vol. 190. P. 114588. doi: 10.1016/j.bcp.2021.114588

81. Ding W.X., Yin X.M. Mitophagy: mechanisms, pathophysiological roles, and analysis // Biol Chem. 2012. Vol. 393, N. 7. P. 547–564. doi: 10.1515/hsz-2012-0119

82. Ezeriņa D., Takano Y., Hanaoka K., et al. N-acetyl cysteine functions as a fast-acting antioxidant by triggering intracellular H_2S and sulfane sulfur production // Cell Chem Biol. 2018. Vol. 25, N. 4. P. 447–459.e4. doi: 10.1016/j.chembiol.2018.01.011

83. Mauthe M., Orhon I., Rocchi C., et al. Chloroquine inhibits autophagic flux by decreasing autophagosome-lysosome fusion // Autophagy. 2018. Vol. 14, N. 8. P. 1435–1455. doi: 10.1080/15548627.2018.1474314

84. Nguyen T.T., Ung T.T., Kim N.H., Jung Y.D. Role of bile acids in colon carcinogenesis // World J Clin Cases. 2018. Vol. 6, N. 13. P. 577–588. doi: 10.12998/wjcc.v6.i13.577

85. NTZ Increases β-catenin Citrullination to Suppress WNT Signaling // Cancer Discov. 2018. Vol. 8, N. 1. P. OF19. doi: 10.1158/2159-8290.CD-RW2017-214

86. Yu J., Yang K., Zheng J., et al. Synergistic tumor inhibition of colon cancer cells by nitazoxanide and obeticholic acid, a farnesoid X receptor ligand // Cancer Gene Ther. 2021. Vol. 28, N. 6. P. 590–601. doi: 10.1038/s41417-020-00239-8

87. Emran T.B., Shahriar A., Mahmud A.R., et al. Multidrug resistance in cancer: understanding molecular mechanisms, immunoprevention and therapeutic approaches // Front Oncol. 2022. Vol. 12. P. 891652. doi: 10.3389/fonc.2022.891652

88. Hodges L.M., Markova S.M., Chinn L.W., et al. Very important pharmacogene summary: ABCB1 (MDR1, P-glycoprotein) // Pharmacogenet Genomics. 2011. Vol. 21, N. 3. P. 152–161. doi: 10.1097/FPC.0b013e3283385a1c

89. Cargnello M., Roux P.P. Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases // Microbiol Mol Biol Rev. 2011. Vol. 75, N. 1. P. 50–83. doi: 10.1128/MMBR.00031-10

90. Hemmati-Dinarvand M., Ahmadvand H., Seghatoleslam A. Nitazoxanide and cancer drug resistance: targeting Wnt/β-catenin signaling pathway // Arch Med Res. 2022. Vol. 53, N. 3. P. 263–270. doi: 10.1016/j.arcmed.2021.12.001

91. Li H., Zeng J., Shen K. PI3K/AKT/mTOR signaling pathway as a therapeutic target for ovarian cancer // Arch Gynecol Obstet. 2014. Vol. 290, N. 6. P. 1067–1078. doi: 10.1007/s00404-014-3377-3

92. Ye C., Wei M., Huang H., et al. Nitazoxanide inhibits osteosarcoma cells growth and metastasis by suppressing AKT/mTOR and Wnt/β-catenin signaling pathways // Biol Chem. 2022. Vol. 403, N. 10. P. 929–943. doi: 10.1515/hsz-2022-0148

93. Karlsson H., Fryknäs M., Senkowski W., et al. Selective radiosensitization by nitazoxanide of quiescent clonogenic colon cancer tumour cells // Oncol Lett. 2022. Vol. 23, N. 4. P. 123. doi: 10.3892/ol.2022.13243

94. Lü Z., Li X., Li K., et al. Nitazoxanide and related thiazolides induce cell death in cancer cells by targeting the 20S proteasome with novel binding modes // Biochem Pharmacol. 2022. Vol. 197. P. 114913. doi: 10.1016/j.bcp.2022.114913

95. Coux O., Tanaka K., Goldberg A.L. Structure and functions of the 20S and 26S proteasomes // Annu Rev Biochem. 1996. Vol. 65. P. 801–847. doi: 10.1146/annurev.bi.65.070196.004101

96. Ghaleb A.M., Nandan M.O., Chanchevalap S., et al. Krüppel-like factors 4 and 5: the yin and yang regulators of cellular proliferation // Cell Res. 2005. Vol. 15, N. 2. P. 92–96. doi: 10.1038/sj.cr.7290271

97. MYBL2 MYB proto-oncogene like 2 [*Homo sapiens* (human)] Gene ID: 4605, updated on 10-Oct-2023

98. Huang Q., Liu M., Zhang D., et al. Nitazoxanide inhibits acetylated KLF5-induced bone metastasis by modulating KLF5 function in prostate cancer // BMC Med. 2023. Vol. 21, N. 1. P. 68. doi: 10.1186/s12916-023-02763-4

AUTHORS' INFO

Vladimir V. Rusanovsky, MD, Dr. Sci. (Medicine), Professor; ORCID: 0000-0002-0432-7946; Scopus Author ID: 57444102200; eLibrary SPIN: 7010-4530; e-mail: rusvv2058@mail.ru

Anastasia A. Saveleva; ORCID: 0009-0009-4997-4045; e-mail: a.a.savel1999@gmail.ru

Zara G. Tadtaeva, MD, Dr. Sci. (Medicine); ORCID: 0000-0002-5809-1457; Scopus Author ID: 57222536682; eLibrary SPIN: 6086-0169; e-mail: tadtaeva2003@mail.ru

Egor S. Astudin; ORCID: 0009-0002-6890-5634; e-mail: astudin-egor.ru@yandex.ru

***Alexandr E. Krivoshein;** address: 2 Litovskaya st., Saint Petersburg, 194100, Russia; ORCID: 0000-0002-4714-1180; e-mail: krivoshein20@mail.ru

Alexandr A. Akimov, MD, Cand. Sci. (Medicine); eLibrary SPIN: 4176-2536; e-mail: laboremus_07@mail.ru

Natalia A. Kuritsina, Cand. Sci. (Biology); ORCID: 0000-0002-0200-5097; eLibrary SPIN: 4361-7365; e-mail: kuritsinana@mail.ru

* Corresponding author / Автор, ответственный за переписку

ОБ АВТОРАХ

Владимир Васильевич Русановский, д-р мед. наук; ORCID: 0000-0002-0432-7946; Scopus Author ID: 57444102200; eLibrary SPIN: 7010-4530; e-mail: rusvv2058@mail.ru

Анастасия Алексеевна Савельева; ORCID: 0009-0009-4997-4045; e-mail: a.a.savel1999@gmail.ru

Зара Григорьевна Тадтаева, д-р мед. наук; ORCID: 0000-0002-5809-1457; Scopus Author ID: 57222536682; eLibrary SPIN: 6086-0169; e-mail: tadtaeva2003@mail.ru

Егор Сергеевич Астудин; ORCID: 0009-0002-6890-5634; e-mail: astudin-egor.ru@yandex.ru

***Александр Евгеньевич Кривошеин;** адрес: Россия, 194100, Санкт-Петербург, ул. Литовская, д. 2; ORCID: 0000-0002-4714-1180; e-mail: krivoshein20@mail.ru

Александр Анатольевич Акимов, канд. мед. наук; eLibrary SPIN: 4176-2536; e-mail: laboremus_07@mail.ru

Наталья Андреевна Курицына, канд. биол. наук; ORCID: 0000-0002-0200-5097; eLibrary SPIN: 4361-7365; e-mail: kuritsinana@mail.ru