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Research Article

The effect of dalargin on growth factors content in experimental ulcerative colitis

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Abstract

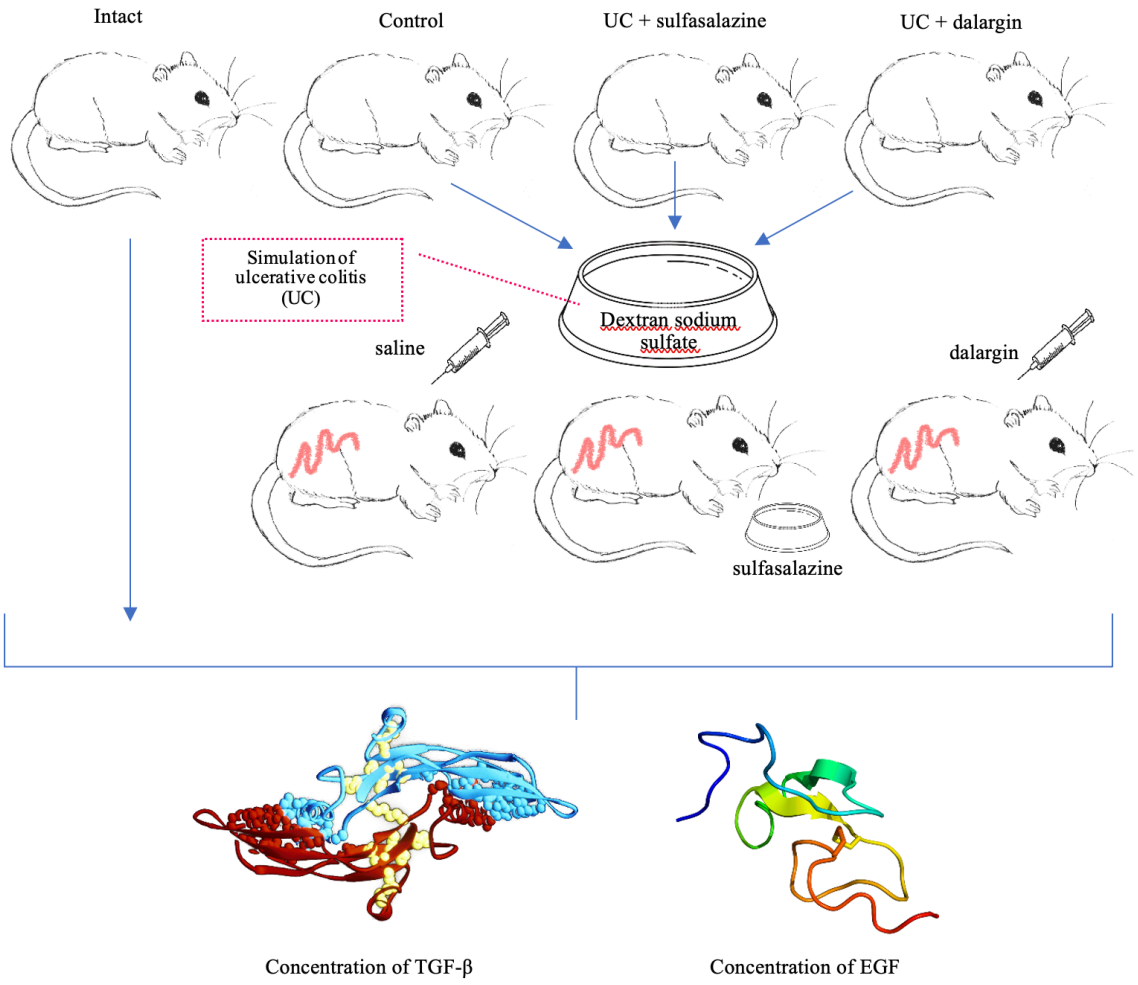
Introduction: The effectiveness of ulcerative colitis (UC) treatment is fairy moderate and it gives a rise to search for new ways of treating it. Considering the combination of dalargin effects, studying the dalargin influence on the UC development is of undoubted interest. **The aim of the study** was to evaluate the dalargin effect on the content of transforming growth factor-β (TGF-β) and epidermal growth factor (EGF) in the colonic wall in mice with experimental ulcerative colitis.

Materials and methods: UC was simulated by replacing water with a 5% solution of dextran sodium sulfate in boiled water for 5 days. The mice were killed on the 5th, 7th and 28th days. The concentrations of TGF-β and EGF in the homogenate of the medial colon were determined by enzyme-linked immunosorbent assay using standard kits.

Results and discussion: The dalargin daily subcutaneous administration (dose of 100 μg/kg) for 7 days led to a decrease in TGF-β levels on the 5th and 7th days compared to the control group. In chronic UC, the concentration of TGF-β was higher than in the control group. The EGF concentration was increased in mice with UC treated with dalargin throughout the experiment. There were no differences in dalargin and sulfasalazine effects on the content of TGF-β, and the concentration of EGF throughout the experiment was significantly higher in the animals treated with dalargin.

Conclusion: Effect of dalargin on the TGF-β and EGF concentrations was explained by its stimulating action to opioid μ-receptors localized on immune cells of the colon.

Graphical abstract



Keywords

ulcerative colitis, dalargin, transforming growth factor-β, epidermal growth factor

Introduction

Ulcerative colitis (UC) is a chronic, relapsing, multifactorial disease of the colon; it has a bimodal pattern of incidence, with the main onset peak between ages 15 and 30 years, and a second smaller peak between ages 50 and 70 years, significantly worsening the quality of life of patients, leading to the development of severe complications and disability of patients (Du and Ha 2020). The pathogenesis of UC is associated with the disruption of the barrier function of the colon mucosa, penetration of luminal microflora into the submucosal layer of the colonic wall, pathological activation of neutrophils, macrophages, dendritic cells, T- and B-lymphocytes and the subsequent development of immune inflammation, causing the ulcers formation and colonic crypts destruction (Le Berre et al. 2023). The effectiveness of modern methods of UC treatment is fairy moderate, which makes it urgent to search for new ways of treating it (Le Berre et al. 2023). Considering the important role of genetic factors in the development of UC, innovative methods, including gene therapy, have an undoubted future (Polikarpova et al. 2022); however, new directions for the use of the already known drugs are also important.

Dalargin was proposed as an antiulcer drug, but currently it is used mainly in the treatment of pancreatitis (Bulgakov 2018). Considering the dalargin effect in the treatment of gastrointestinal tract diseases, as well as the immunomodulatory and antioxidant effects of the drug (Bulgakov 2018; Platonova et al. 2018), studying the dalargin effect on the UC development is of undoubted interest. Previously, we established its medicinal effect in experimental UC in mice, manifested by a decrease in the index of disease activity, the reduction in ulcers and

infiltrates in the colonic wall (Liashev et al. 2023). But the mechanism of the pharmacological dalargin effect in UC is unknown.

The participation of transforming growth factor-β (TGF-β) and epidermal growth factor (EGF) in the UC development has been confirmed. TGF-β is a family of pleiotropic cytokines produced by various immune and epithelial cells, fibroblasts (Zhao et al. 2020; Chandiran and Cauley 2023). In the colon, TGF-β suppresses the development of the immune response to antigens of luminal microflora and takes part in the immunological tolerance formation (Yun et al. 2019; Triantafillidis et al. 2020). It was previously shown that TGF-β promotes reparative processes in the mucous membrane of the colon in UC (Tatiya-Aphiradee et al. 2018); however, its excess production can contribute to the fibrosis development in the colonic wall (Naghdalipour et al. 2022), leading to the formation of strictures requiring surgery. It has been established that functional activity of TGF-β in animals with experimental UC and patients with inflammatory bowel disease is impaired, and its correction can be considered as a potential way to treat UC (Tatiya-Aphiradee et al. 2022).

EGF is synthesized by intestinal epithelial cells during inflammation and binds to specific receptors (EGFR) (Lu et al. 2014). EGF has a pronounced stimulating effect on the migration and proliferation of fibroblasts, which helps to restore the colonic barrier. The cytokine suppresses the immune response to luminal microbiota antigens, reducing the severity of colon damage in UC. Activation of EGFR has an effect on the UC development, indicating the possibility of using EGF as a means of UC treating (Lu et al. 2014).

Thus, studying the dalargin effect, as a potential treatment for UC, on the content of TGF-β and EGF in the wall of the medial colon is of undoubted interest.

The aim of the study was to evaluate the dalargin effect on the content of transforming growth factor-β and epidermal growth factor in the colonic wall in mice with experimental ulcerative colitis.

Materials and methods

Drugs

Dalargin (Tir-D-Ala-Gly-Phen-Leu-Arg) (NPO Microgen, Russia) was dissolved in a 0.9% sodium chloride solution, applied subcutaneously in a volume of 0.1 mL daily at a dose of 100 μg/kg body weight once a day for 7 days from the beginning of UC simulation. As shown earlier, dalargin manifested high pharmacological activity at the indicated dose (Lishmanov et al. 2012). Sulfasalazine (KRKA, Slovenia) was used as a reference drug and administered intragastrically to mice in the suspension form in physiological solution at a dose of 200 mg/kg body weight in a volume of 0.3 mL for 7 days from the beginning of UC simulation (Motov et al. 2021). The treatment of experimental UC in rats with intragastric sulfasalazine administration at a dose of 200 mg/kg decreased the disease activity index, the area of ulcers and hemorrhages in the rectum, and the content of induced NO-synthase, IL-1β, IL-6, TNFα in the rectal homogenate (Zhu et al. 2019; Motov et al. 2021).

Dextran sodium sulfate (DSS) (Mr=40000) was purchased from PanReac-AppliChem (Germany).

Animals

Male Balb/C mice weighing 20-23 g were purchased from the Stolbovaya branch of the Federal State Budgetary Institution of Science "Scientific Center for Biomedical Technologies of the Federal Medical and Biological Agency". All mice were housed 7/cage and were fed standard laboratory chow in an animal room with 12 h dark/light cycles at a constant temperature of 20±5°C. All animal experiments were conducted in the Laboratory of Preclinical trials of Drugs of the Research Institute of Experimental Medicine of Kursk State Medical University under guidelines of humane treatment of laboratory animals (Lipatov et al. 2019a, 2019b), the Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 and the Rules of Good Laboratory Practice in the Russian Federation (order of the Ministry of Health of the Russian Federation No. 199n dated April 1, 2016. The experiments were approved by the Regional Ethics Committee (REC) (Minutes No. 1 of April 3 2023).

Experimental design

The investigation was carried out on 67 male Balb/C mice, 4 of which were intact. UC was simulated in 63 remaining mice. All UC animals were randomly divided in 3 experimental groups: 1) control (UC+saline, n=21); 2) experimental No. 1 (UC+dalargin solution, n=21); 3) experimental No. 2 (UC+sulfasalazine, n=21). Seven mice from each group were killed by cervical dislocation under the chloral hydrate anesthesia (Macklin, China) on the 5th, 7th and 28th days. Considering that dalargin and sulfasalazine were administered to animals in different ways, the control group included 12 mice treated with saline subcutaneously and 9 mice administered with intragastric saline, and therefore 4 mice treated with saline subcutaneously and 3 mice treated with saline intragastrically were killed on each days. It was established earlier there were neither clinical nor morphological differences between Balb/C mice with experimental UC treated with saline in the indicated ways at all stages of the experiment (Garo et al. 2019). Saline was administered once a day for 7 days from the beginning of UC simulation in a volume of 0.1 mL subcutaneously or 0.3 mL intragastrically.

Research methods

UC was simulated by replacing drinking water with a 5% solution of DSS in boiled water for 5 days (Naghdalipour et al. 2022). Earlier, the development of acute UC was shown on the 5th and 7th days, and chronic colitis on the 28th day after the beginning of DSS solution drinking (Khomyakova et al. 2013). Early morphological studies confirmed UC development in animals after drinking a 5% DSS solution (Liashev et al. 2023). The mice were killed by cervical dislocation under chloral hydrate anesthesia on the 5th, 7th and 28th days; the colon was removed, then opened with a longitudinal incision along the edge of the mesentery attachment, washed with phosphate-buffered saline (pH=7.4, 0.01 M), and the medial section was isolated and tissue (50 mg) was homogenized in a Potter-Elweheim homogenizer for 10 minutes. The homogenate was centrifuged in an SL-16R centrifuge (Thermo Fisher Scientific, Germany) for 10 minutes at 3000 rpm. After centrifugation, the supernatant was collected in test tubes, frozen at t=-40°C and stored

for no longer than 2 months. The concentrations of TGF-β and EGF in the homogenate of the medial colon were determined by enzyme-linked immunosorbent assay (ELISA) using standard kits from Cloud-Clone Corp. (China) on a Lazurit automatic enzyme immunoassay analyzer (Dynex Technologies, USA), according to the instructions.

Statistical data processing

Statistical analysis of the biochemical results was carried out using Statistica software version 10 (USA). All samples were tested for the type of distribution using the Shapiro-Wilk W-test. The results were described as a median (Me), lower and upper quartiles (Q1 and Q3, respectively) due to the absence of a normal distribution in most ordered samples. Mann-Whitney U-test was used to determine the significance of the differences. The null hypothesis was rejected at the level of statistical significance $p<0.05$.

Results and discussion

UC simulation in male Balb/C mice led to an increase in the TGF-β content in the homogenate of the medial colon on the 5th and 7th days of the experiment (acute UC) by 4.3 and 3.9 times, respectively (P=0.0107), compared with the intact group (Table 1). There were no significant differences in the TGF-β content on the 28th day (chronic UC), between the intact and control groups (P=0.2193). There were no significant differences between the intact and control groups in the EGF content on the 5th of UC simulation in the homogenate of the medial colon (P=0.0890). The EGF concentration increased by 29.6% and 3.4 times (P=0.0107) on the 7th and 28th days of the experiment.

The dalargin administration led to a decrease in TGF-β levels on the 5th and 7th days of the experiment compared to the control group by 49.4% and 45.8% (P=0.0022), respectively. In chronic UC, the concentration of TGF-β was higher than in the control group – by 40.4% (P=0.0212). An increase in the EGF concentration was also found in mice with UC treated with dalargin throughout the experiment: on the 5th day – by 91.7% (P=0.0022), on the 7th day – by 2.4 times (P=0.0022), and on the 28th – by 2.9 times (P=0.0022).

A decrease in TGF-β levels was shown on the 5th and 7th days after the beginning of UC simulation by 36.4% and 48.5%, respectively (P=0.0022) in the group treated with sulfasalazine, and in the level of EGF on the 7th – only by 40.2% (P=0.0033). There were no significant differences in the concentrations of both growth factors in other periods.

Comparing the effects of dalargin and sulfasalazine on the content in TGF-β and EGF in the homogenate of the medial colon revealed the absence of significant differences in the TGF-β content, and the EGF concentration throughout the experiment was significantly higher in animals treated with dalargin. The EGF content was higher in the group treated with dalargin compared to animals treated with sulfasalazine by 95.75% (P=0.0049) on the 5th day, by 69.7% – on the 7th day (P=0.0022), by 3.3 times – on the 28th day (P=0.0022).

The results obtained confirm the literature data on a TGF-β increase in both laboratory animals with experimental colitis and in patients with UC (Zhu et al. 2019; Naghdalipour et al. 2022). However, some studies showed a TGF-β decrease in the homogenate of the colon of mice with experimental UC (Luo et al. 2019; Liu et al. 2021). Such results can be explained by the development of UC of various severity in laboratory animals, since different murine strains have different resistance to factors provoking UC (Khomyakova et al. 2013). According to many researchers, TGF-β plays a key role in the development of inflammation in the colon (Yun et al. 2019). The TGF-β-Smad signaling pathway is the most important in the implementation of the anti-inflammatory TGF-β effect, since it regulates the Th17/Treg balance (Liu et al. 2021). It is known that activated Th17-cells accumulate in the colonic wall in UC and produce proinflammatory cytokines, including IL-17A, IL-17F, and IL-21.

In contrast, Tregs secrete IL-6 and TGF-β, suppressing Th17 activity (Liu et al. 2021). The TGF-β-Smad signaling pathway controls the differentiation of Th17 and Treg: TGF-β in low concentration enhances IL-6 and IL-17 effects, promoting Th17-cells differentiation, and TGF-β in high concentration enhances Treg differentiation (Liu et al. 2021). It was previously shown that a significant increase in the TGF-β concentration led to activation of the TGF-β-Smad signaling pathway, an increase in the activity of Smad7, which is accompanied by a decrease in the anti-inflammatory TGF-β effect (Garo et al. 2019). In addition, it was found that Smad7 suppression inhibits the activity of epithelial myosin light chain kinase and causes a decrease in the permeability of the epithelial barrier of the colonic mucosa (Bai et al. 2022).

An increase in the EGF content was established on the 7th and 28th days of the experimental UC development. The medicinal effect of an EGF analogue on the UC development was shown earlier (Zhou et al. 2022). It has been established that activation of EGF receptors on colonic epithelial cells has a cytoprotective effect and also suppresses the production of nuclear factor kB, TNFα and interferon-γ by macrophages (Lu et al. 2014). There is evidence of the conjugation of the effects of TGF-β and EGF through the pro-inflammatory signaling pathway TGF-β-EGF receptor (El Mahdy et al. 2023), with drug effects associated, among other things, with inhibition of this mechanism.

The dalargin administration intramuscularly at a dose of 100 mcg/kg once a day for 7 days had a corrective effect on the TGF-β content in the homogenate of the medial colon in mice with experimental UC: the TGF-β concentration was significantly lower on the 5th and 7th days, and it was higher compared to the control group on the 28th day. The EGF content increased throughout the experiment in UC+dalargin group.

Dalargin is a leu-enkephalin analogue manifesting affinity for opioid μ- and δ-receptors (Bulgakov 2018). Opioid μ-type receptors are present on neutrophils, macrophages, dendritic cells, T and B lymphocytes in the colonic wall (Raeeszadeh-Sarmazdeh et al. 2020). An increase in the expression of opioid μ-receptor mRNA has been established during the acute period of UC. The normal expression of opioid μ-receptor mRNA was observed in the chronic UC (Lashgari et al. 2021). These data indicate the involvement of opioid μ-receptors in the regulation of inflammation in the colon. The use of the enkephalinase inhibitor opiorphin in experimental UC in mice caused a decrease in the concentration of pro-inflammatory cytokines (IL-1β, IL-6, TNFα) and an

Table 1. Effect of dalargin on the concentrations of transforming growth factor-β and epidermal growth factor in the homogenate of the medial colon

Group	Indicators		
	Duration of experiment, days	**TGF-β content in colon homogenate (pg/mg tissue protein)**	**EGF content in colon homogenate (pg/mg tissue protein)**
Intact		373.0 [203.0; 520.0]	24.0 [22.4; 27.5] P=0.7768
Control group (UC+saline)	the 5th day	1620.0 [1550.0; 2510.0]^{x} P=0.0107	24.0 [24.0; 27.0] P=0.0890
	the 7th day	1440.0 [1410.0; 1500.0]^{x} P=0.0107	31.1 [25.0; 38.0] P=0.0107^{x}
	the 28th day	520.0 [430.0; 580.0] P=0.2193	82.0 [71.0; 91.0] P=0.0107^{x}
Group of ulcerative colitis+dalargin at a dose 100 μg/kg	the 5th day	820.0 [801.0; 950.0]* P=0.0022 P=0.0553	46.0 [38.8; 51.0]*^{1} P=0.0022 P=0.0049
	the 7th day	780.0 [722.0; 800.0]* P=0.0022 P=0.7983	74.0 [73.0; 76.7]*^{1} P=0.0022 P=0.0022
	the 28th day	730.0 [540.0; 760.0]* P=0.0212 P=0.0845	
Group of ulcerative colitis+sulfasalazine at a dose 200 mg/kg	the 5th day	1030.0 [841.0; 1190.0]* P=0.0022	23.5 [7; 26] P=0.3067
	the 7th day	742.0 [730.0; 788.0] P=0.0022	43.6 [39.9; 49.6] P=0.0033*
	the 28th day	574.0 [490.0; 720.0] P=0.6093	73.1 [59.9; 78.7] P=0.3067

Note: ^{x} – p<0.05 compared to the intact group; *– p<0.05 compared to the control group; ^{1} – p<0.05 compared to the ulcerative colitis + sulfasalazine group.

increase in the content of anti-inflammatory IL-10, both in the colonic wall and in the plasma, as well as a decrease in the activity index disease and reduction in the area of ulcers of the colonic mucosa (Luo et al. 2022).

Thus, an increase in leu- and met-enkephalins content in the blood plasma, as well as an increase in the expression and activity of opioid μ-receptors in opiorphin administration, led to the suppression of the activity of nuclear factor kB, p65 protein, and Toll-like receptor (TLR-4), induced NO-synthase and cyclooxygenase type 2 (Raeeszadeh-Sarmazdeh et al. 2020). The involvement of opioid μ-receptors in the anti-inflammatory effect of opiorphin was confirmed by the fact that these effects were not observed in naloxone administration, which blocks the activity of opioid μ-receptors (Luo et al. 2022).

Conclusion

Thus, the study established that the dalargin administration had a corrective effect on the TGF-β content and a stimulating effect on the EGF concentration in the homogenate of the medial colon in mice with experimental UC. Dalargin effect of on EGF was significantly higher than the effect of sulfasalazine throughout the experiment. No significant differences were established between the effects of dalargin and sulfasalazine on the TGF-β content. Apparently, the pharmacological dalargin effect on TGF-β and EGF concentrations was explained by its stimulating effect on opioid μ-receptors localized on macrophages, neutrophils, and lymphocytes of the colonic wall.

A decrease in TGF-β activity under dalargin influence inhibits the activity of Smad7, which contributes to the anti-inflammatory TGF-β effect. An increase in EGF activity in the group treated with dalargin enhanced reparative processes in the colon and corrected the permeability of the colonic barrier. The results obtained open up prospects for dalargin as a drug of choice for the UC treatment, including its combination with other drugs.

Conflict of interest

The authors declare the absence of a conflict of interests.

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The authors have no funding to report.

Data availability

All of the data that support the findings of this study are available in the main text.

References

- Bai B, Li H, Han L, Mei Y, Hu C, Mei Q, Xu J, Liu X (2022) Molecular mechanism of the TGF-β/Smad7 signaling pathway in ulcerative colitis. Molecular Medicine Reports 25 (4): 116. https://doi.org/10.3892/mmr.2022.12632 [PubMed]
- Bulgakov SA (2018) Peptide therapeutics in pancreatology. Russian Journal of Evidence-based Gastroenterology [Dokazatel'naya Gastroenterologiya] 7(4): 30–34. https://doi.org/10.17116/dokgastro2018704130 [in Russian]
- Chandiran K, Cauley LS (2023) The diverse effects of transforming growth factor-β and SMAD signaling pathway during the CTL response. Frontiers in Immunology 14: 1199671. https://doi.org/10.3389/fimmu.2023.1199671 [PubMed] [PMC]
- Du L, Ha C (2020) Epidemiology and pathogenesis of ulcerative colitis. Gastroenterology Clinics of North America 49(4): 643–654. https://doi.org/10.1016/j.gtc.2020.07.005 [PubMed]
- El Mahdy RN, Nader MA, Helal MG, Abu-Risha SE, Abdelmageed ME (2023) Eicosapentaenoic acid mitigates ulcerative colitis-induced by acetic acid through modulation of NF-κB and TGF-β/EGFR signaling pathways. Life Science 327: 121820 https://doi.org/10.1016/lfs.2023.121820 [PubMed]
- Garo LP, Ajay AK, Fujiwara M, Beynon V, Kuhn S, Gabriely G, Sadhukan S, Raheja R, Rubino S, Weiner HL, Murugaiyan G (2019) Smad7 controls immunoregulatory PDL2/1-PD1 signaling in intestinal inflammation and autoimmunity. Cell Reports 28(13): 3353–3366. https://doi.org/10.1016/j.celrep.2019.07.065 [PubMed] [PMC]
- Khomyakova TI, Zolotova NA, Khochanskiy DN, Khomyakov YuN (2013) The modelling of acute and chronic colitis in mice. Treatment and prophylaxis [Lecheniye i Profilaktika] 7(3): 148–159. [in Russian]
- Lashgari N-A, Roudsari NM, Zandi N, Pazoki B, Rezaei A, Hashemi M, Momtaz M, Rahimi R, Shayan M, Dehpour AR, Abdolghaffari AH (2021) Current overview of opioids in progression of inflammatory bowel disease; pharmacological and clinical considerations. Molecular Biology Reports 48(1): 855–874. https://doi.org/10.1007/s11033-020-06095-x [PubMed]
- Le Berre C, Honap S, Peyrin-Biroulet L (2023) Ulcerative colitis. Lancet 402(10401): 571–584. https://doi.org/10.1016/S0140-6736(23)00966-2 [PubMed]
- Liashev AYu, Mal GS, Solin AV (2023) Investigation of dalargin effectiveness in experimental ulcerative colitis. Experimental and Clinical Pharmacology [Eksperimental'naya i Klinicheskaya Farmacologiya 86(9): 7–11. http://doi.org/10.30906/0869-2092-2023-86-9-7-11 [in Russian]
- Liu X, Sun Z, Wang H (2021) Metformin alleviates experimental colitis in mice by up-regulating TGF-β signaling. Biotechnic and Histochemistry 96(2): 146–152. https://doi.org/10.1080/10520295.2020.1776896 [PubMed]
- Lipatov VA, Severinov DA, Kryukov AA, Saakyan AR (2019a) Ethical and legal aspects of in vivo experimental biomedical research. Part I. I.P. Pavlov Russian Medical Biological Herald [Rossiiskii Medico-Biologicheskii Vestnik Imeni Akademika I.P. Pavlova] 27 (1): 80-92. https://doi.org/10.23888/PAVLOVJ201927180-92 [in Russian]
- Lipatov VA, Severinov DA, Kryukov AA, Saakyan AR (2019b) Ethical and legal aspects of in vivo experimental biomedical research. Part II. I.P. Pavlov Russian Medical Biological Herald [Rossiiskii Medico-Biologicheskii Vestnik Imeni Akademika I.P. Pavlova] 27(2): 245–257. https://doi.org/10.23888/PAVLOVJ2019272245-257 [in Russian]
- Lishmanov YuB, Maslov LN, Naryzhnaya NV, Pei J-M, Kolar F, Zhang Y, Portnichenko AG, Wang H (2012) Endogenous opioid system as a mediator of acute and long-term adaptation to stress. Prospects for clinical use of opioid peptides. Annals of the Russian Academy of Medical Sciences [Vestnic Rossiiskoi Akademii Meditsinskikh Nauk] 6: 73–82. [in Russian]
- Lu N, Wang L, Cao H, Liu L, Kaer LV, Washington MK, Rosen MJ, Dube PE, Wilson KT, Ren X, Hao X, Polk DB, Yan F (2014) Activation of the epidermal growth factor receptor in macrophages regulates cytokine production and experimental colitis. Journal of Immunology 192 (3): 1013-1023. https://doi.org/10.4049/jimmunol.1300133 [PubMed] [PMC]
- Luo P, Li X, Gao Y, Zhang Q, Wang Z, Tian X (2022) Central administration of human opiorphin alleviates dextran sodium sulfate-induced colitis in mice through activation of the endogenous opioid system. Frontiers of Pharmacology 13: 904926. https://doi.org/10.3389/fphar.2022.904926 [PubMed] [PMC]
- Luo S, Wen R, Wang Q, Zhao Z, Nong F, Fu Y, Huang S, Chen J, Zhou L, Luo X (2019) Rhubarb peony decoction ameliorates ulcerative colitis in mice by regulating gut microbiota to restoring Th17/Treg balance. Journal of Ethnopharmacology 231: 39–49. https://doi.org/10.1016/j.jep.2018.08.033 [PubMed]
- Motov VS, Bykova AV, Bykov VV, Khazanov VA, Vengerovskii AI (2021) Protective activity of aminoguanidine derivate on the model of ulcerative colitis in rats. Experimental and Clinical Pharmacology [Eksperimental'naya i Klinicheskaya Farmakologiya] 84(5): 6–10. http://doi.org/10.30906/0869-2092-2021-84-5-6-10 [in Russian]
- Naghdalipour M, Moradi N, Fadaei R, Barez SR, Sayyahfar S, Mokhtare M, Fallah S, Esteghamati A (2022) Alteration of miR-21, miR-433 and miR-590 tissue expression related to the TGF-β signaling pathway in ulcerative colitis patients. Archives of Physiology and Biochemistry 128(5): 1170–1174. https://doi.org/10.1080/13813455.2020.1762656 [PubMed]
- Platonova VV, Sevbitov AV, Shakaryants AA, Dorofeev AE (2018) The experimental clinical substantiation of treatment of patients with odontogenic phlegmon of maxillofacial area using Dalargin in complex therapy. Clinical and Laboratory Diagnics [Klinicheskaya i Laboratornaya Diagnostika] 63 (5): 293–296. https://doi.org/10.18821/0869-2084-2018-63-5-293-296 [PubMed] [in Russian]
- Polikarpova AV, Egorova TV, Bardina MV (2022) Genetically modified animal models of hereditary diseases for testing of gene-directed therapy. Research Results in Pharmacology 8(2): 11–26. https://doi.org/10.3897/rrpharmacology.8.82618
- Raeeszadeh-Sarmazdeh M, Do LD, Hritz BG (2020) Metalloproteinases and their inhibitors: potential for the development of new therapeutics. Cell 9(5): 1313. https://doi.org/10.3390/cell9051313 [PubMed] [PMC]
- Tatiya-Aphiradee N, Chatuphonprasert W, Jarukamjorn K (2018) Immune response and inflammatory pathway of ulcerative colitis. Journal of Basic and Clinical Physiology and Pharmacology 30(1): 1–10. https://doi.org/10.1515/jbcpp-2018-0036 [PubMed]
- Triantafillidis JK, Tzouvala M, Triantafyllidi E (2020) Enteral nutrition supplemented with transforming growth factor-β, colostrum, probiotics, and other nutritional compounds in the treatment of patients with inflammatory bowel disease. Nutrients 12(4): 1048. https://doi.org/10.3390/nu12041048 [PubMed] [PMC]
- Yun S-M, Kim S-H, Kim E-H (2019) The molecular mechanism of transforming growth factor-β signaling for intestinal fibrosis: A mini-review. Frontiers in Pharmacology 10: 162. https://doi.org/10.3389/fphar.2019.00162 [PubMed] [PMC]
- Zhao D, Cai C, Chen Q, Jin S, Yang B, Li N (2020) High-fat diet promotes DSS-Induced ulcerative colitis by downregulated FXR expression through the TGFB pathway. BioMed Research International 2020: 3516128. https://doi.org/10.1155/2020/3516128 [PubMed] [PMC]
- Zhou L, Zhou W, Joseph AM, Chu C, Putzel GG, Fang B, Teng F, Lyu M, Yano H, Andreasson KI, Mekada E, Eberl G, Sonnenberg GF (2022) Group 3 innate lymphoid cells produce the growth factor HB-EGF to protect the intestine from TNF-mediated inflammation. National Immunology 23(2): 251–261. https://doi.org/10.1038/s41590-021-01110-0 [PubMed] [PMC]
- Zhu L, Gu P-Q, Shen H (2019) Protective effects of berberine hydrochloride on DSS- induced ulcerative colitis in rats. International Immunopharmacology 68: 242–251. http://doi.org/10.1016/j.intinp.2018.12.036 [PubMed]

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