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EFFECT OF PYRROLE DERIVATIVES ON MANIFESTATION OF INFLAMMATION IN RATS WITH CHRONIC ULCERATIVE COLITIS UNDER PREDNISOLONE TREATMENT

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Background. Previously, we have detected the antitumor and anti-inflammatory activities of pyrrole-derived protein kinase inhibitors – MI-1 (1-(4-Cl-benzyl)-3-Cl-4-(CF₃-phenylamino)-1H-pyrrole-2,5-dione 1) and D1 (5-amino-4-(1,3-benzothiazole-2-yl)-1-(3-methoxyphenyl)-1,2-dihydro-3H-pyrrole-3-one) using the rat colon cancer model. Therefore, pyrrole derivatives were targeted at detecting the anti-inflammatory effect on the model of ulcerative colitis caused by acetic acid in rats.

Materials and Methods. Prednisolone was used as a reference anti-inflammatory drug of glucocorticoid nature. It was administered intraperitoneally at a dose of 0.7 mg/kg. The compounds were administered 2 h after the first administration of acetic acid. Total protein was estimated quantitatively, as described by Lowry *et al.*, 1951. The content of malonic dialdehyde, protein carbonyl groups, and the activity of antioxidant enzymes as indicators of colon mucosa redox status were measured spectrophotometrically. Statistical analysis of the results was performed using MS Excel-2013.

Results and Discussion. In case of chronic colitis, the number of carbonyl groups and lipid peroxidation products in the colonic mucosa is increased, indicating the development of oxidative stress. Administration of pyrrole derivatives separately contributes to approaching normal levels of these indicators. Adding prednisolone does not cause this effect. A decrease in superoxide dismutase activity was detected under colitis, which is a typical phenomenon for chronic inflammation and may indicate a depletion of the enzyme.

In case of colitis, alanine aminotransferase activity and the content of direct bilirubin are increased, which indicates a liver injury and is a systemic manifestation of the



colon inflammation. Pyrrole derivatives help to reduce the liver injury, which indicates a restoration of normal alanine aminotransferase activity and direct bilirubin content.

Conclusion. It has been found that at chronic colitis pyrrole derivatives reduce manifestations of inflammation and contribute to the restoration of the normal structure of the mucous membrane (comparative to prednisolone as a standard anti-inflammatory drug), which suggests their anti-inflammatory effectiveness. At the same time, an increase in total bilirubin under exposition to pyrrole derivatives may be a sign of adverse effects on the rats' liver.

Keywords: experimental colitis, prednisolone, pyrrole derivative, mucosa descending colon

INTRODUCTION

Inflammatory bowel disease (IBD) which includes ulcerative colitis (UC) is one of the most serious and currently unsolved problems in modern gastroenterology. In terms of severity and frequency of complications, IBD occupies the leading position among gastrointestinal tract diseases [3]. The etiology of IBD is still not fully understood. It is probably of an autoimmune nature, and the main causes are considered to be hereditary predisposition, allergic reactions, nutrition, etc. [3].

Due to the fact that tumor growth is usually accompanied by inflammation of tumor nodules in adjacent apparently normal tissue [1] and prolonged pharmaceutical suppression of inflammation significantly reduces the risk of tumor development [6], chronic UC is considered as a precursor condition for tumorigenesis. Moreover, the rate of colorectal cancer cases among people with UC history exceeding 10 years increases eightfold compared to the average population [1].

Protein kinase inhibitor pyrrole derivatives 1-(4-Cl-benzyl)-3-Cl-4-(CF₃-phenylamino)-1H-pyrrol-2,5-dione (MI-1) and 5-amino-4-(1,3-benzothiazole-2-yl)-1-(3-methoxyphenyl)-1,2-dihydro-3H-pyrrole-3-one (D1) have been synthesized at the Chemistry Department of Taras Shevchenko National University of Kyiv. A complex study of biologically active pyrrole derivatives concerning their anti-inflammatory effects on colonic mucosa on the experimental ulcerative colitis model and possible mechanisms of their action has not been performed. Pyrrole derivatives can inhibit such protein kinases as Yes, Src(h), ZAP70, Syk(h), PDK1, EGFR, IGF-1R, VEGFR [14, 21]. These substances reveal anti-proliferative and proapoptotic action toward malignant cells without significant effects on the proliferation and survival of normal cells [14, 21].

MATERIALS AND METHODS

96 white male Wistar rats with an average body weight of 213 g (10 weeks old) were used for the study. Rats were kept in standard vivarium conditions under natural lightning with free access to tap water and standard rodent chow. The research was conducted in accordance with the principles of bioethics, legislation and requirements in accordance with the provisions of the European Convention for the Protection of Vertebrate Animals used for Research and Scientific Purposes (Strasbourg, 1986) and the General Ethical Principles of Animal Experiments adopted by the First National Congress on Bioethics (Kyiv, 2001) as well as approved by the Ethics Committee of Taras Shevchenko National University of Kyiv, Ukraine (Protocol No. 02-03-2021 of March 4, 2021).

Experimental model of ulcerative colitis was simulated by a double rectal administration of 1 mL 4% acetic acid solution weekly during 2 weeks [20]. Previously, the animal colons were cleaned by rectal administration of 2–3 mL of saline, followed by a massage of the lower abdomen to facilitate defecation for 10–15 min before the introduction of acetic acid. MI-1 and D1 were administered in conditionally effective doses (2.7 mg/kg and 2.3 mg/kg, respectively) [13] *per os* daily starting 2 h after the first acetic acid administration. Reference prednisolone (therapeutic, which is commonly used against UC of moderate severity [20]) was injected intraperitoneally at a dose of 0.7 mg/kg at the same schedule. Control animals received appropriate solvents.

Experimental groups: group I – Control (n = 5); group II – Colitis (n = 7); group III – Control + D1 (n = 7); group IV – Colitis + D1 (n = 7); group V – Control + MI-1 (n = 7); group VI – Colitis + MI-1 (n = 7); group VII – Colitis + D1 + MI-1 (n = 7); group VIII – Control + prednisolone (n = 7); group IX – Colitis + prednisolone (n = 7); group X – Control + prednisolone + D1 (n = 7); group XI – Colitis + prednisolone + D1 (n = 7); group XII – Control + prednisolone + MI-1 (n = 7); group XIII – Colitis + prednisolone + MI-1 (n = 7); group XIV – Colitis + prednisolone + D1 + MI-1 (n = 7).

The internal surfaces of the intestines were washed with saline followed by PBS containing 1 mM of EDTA and 0.4 mM of PMSE (phenylmethanesulfonylfluoride) with a pH of 7.0. Then, the mucosa was scratched and quickly frozen to -68 °C. After defrosting, the samples were smoothly homogenized in 1 mM EDTA and 0.4 m PBS and centrifuged at 1000 g for 15 min, and supernatants were gathered and used for analysis. The total protein was estimated in a quantitative manner as described by Lowry *et al.* [12]. Malonic dialdehyde (MDA) [2], protein carbonyl groups (PCG) [11], intracellular superoxide dismutase (SOD, EC 1.15.1.1) [3, 5], and catalase (CAT, EC. 1.11.1.6) [2, 4] activities as indicators of redox status were measured spectrophotometrically. The intracellular enzymes alanine aminotransferase (ALT, EC. 2.6.1.2) and aspartate aminotransferase (ACT, EC. 2.6.1.1) activities and the concentration of total and direct bilirubin was measured in blood serum with the use of sets of Reagent Company (Ukraine). For this purpose, blood was maintained at room temperature for 30 min, centrifuged at 1000 g for 10 min, and then serum was collected in a separate test tube.

The mucosal lesions were scored using 11-grade scale, where total grade was calculated as a sum of grades: 0–3 grades – bowel mucosa integrity disorders, 0–3 grades – leucocytic infiltration, 0–3 grades – muscle layer thickening, 0–1 grade – crypt abscesses formation, and 0–1 grades – goblet cells decrease [8].

Statistical analysis of the results was performed using MS Excel-2013.

RESULTS

Morpho-functional changes in the colonic mucosa under chronic ulcerative colitis. Under chronic ulcerative colitis, intestinal wall was thickened and irritated, adhesions between loops of the intestine and necrotic masses on its surface were detected under visual inspection. At the same time, diffuse epithelium desquamation and signs of inflammation were observed using light microscopy, indicating the development of ulcerative colitis. When both pyrrole derivatives were applied, the manifestations of inflammation decreased, the structure of the colonic mucosa appeared to be normal as well as in the case of prednisolone treatment. The observed changes could indicate the anti-inflammatory efficacy of the tested protein kinase inhibitors.

The combined effect of prednisolone and MI-1 at the macro level was the same as that of MI-1 alone. The signs of inflammation manifested by oedema and microvasculature disorders were close to the level of the prednisolone group, epithelial desquamation disappeared. The total damage score was 2.5 points (**Table**). Thus, under the combined action of prednisolone and MI-1, the effect was more pronounced than that under the action of prednisolone alone but less pronounced than under the action of MI-1 alone.

Table. The degree of intestinal damage and the intensity of the inflammatory process in colonic mucosa of rats with UC treated with prednisolone, MI-1 and D1

Таблиця. Ступінь пошкодження кишки й інтенсивність запального процесу в товстій кишці щурів за дії преднізолону, MI-1 та D1 за виразкового коліту

Experimental groups	Intestinal damage (at the macro level)	Intensity of inflammation (at the micro level)
Control	0	0
Colitis	3.8±0.5*	7.3±0.8*
Colitis + Prednisolone	0	4.5±0.4*
Colitis + MI	0	2.5±0.2*
Colitis + D1	0	2.5±0.4*
Colitis + MI-1 + D1	2.5±0.4*	3.2±0.4*
Colitis + Prednisolone + MI-1	0	5.5±0.3*
Colitis + Prednisolone + D1	2.9±0.2*	6.0±0.3*
Colitis + Prednisolone + MI-1 + D1	4.3±0.6*	6.5±0.5*

Comment: * – $p \leq 0.05$ compared with control, the absence of damage in the control is taken as 0 [3, 4]

Примітка: * – $p \leq 0,05$ порівняно з контролем, відсутність пошкоджень у контролі прийнято за 0 [3, 4]

The degree of intestinal damage in D1 + prednisolone-treated animals corresponded to that of the D1-treated group. However, at the micro-level, the inflammatory process intensified, namely: oedema, vascular disorders were more pronounced comparative to the action of D1 alone (**Table**). Therefore, the combined action of prednisolone + D1 was less effective than the separate effect of each compound. Mucosal damage micro-score approximately reached the value of the colitis group (**Table**). Therefore, the total positive effect of these compounds was offset by their negative impact, which may be due to the suppression of not only inflammatory but also regenerative processes.

Under the influence of all compounds together (prednisolone + MI-1 + D1), the total damage to rat's colons at the macro level corresponded to 10.8 points and approximately reached the value of the colitis group (**Table**). Therefore, the total positive effect of these compounds was apparently absent.

Prooxidant-antioxidant balance of colonic mucosa in rats with chronic ulcerative colitis treated with both pyrrole derivatives and prednisolone. An increase in the amount of superoxide radicals and the activation of lipid peroxidation (LPO) processes accompanied by the activation of protein oxidation is often observed under acute and chronic inflammation [2]. Oxidative modification of proteins (OMP) can lead to protein fragmentation with the formation of low molecular weight components or aggregation of protein molecules [4]. As a result, the proteins conformation changes,

which can be crucial for the catalytic activity of enzymes. Moreover, moderately oxidized proteins are usually more sensitive to proteolysis [4]. Initiation of the OMP process is the most dangerous part of toxic cell damage due to the inactivation of cytoplasmic enzymes and membrane ion pumps, followed by the launch of various mechanisms of cell destruction [2].

In rats with UC, the content of OMP increased by 30%, accompanied with similar increasing in MDA content (almost twice compared with control). Combined action of MI-1 and D1 reduced OMP content by 10% compared with UC-group. Moreover, at the combination of both pyrrole derivatives with prednisolone (MI-1 + D1 + P-treated UC-rats) the content of OMP decreased even more (by 30% compared with control) (Fig. 1). Then, the combined action of MI-1+D1+P reduced the content of TBA-active products by 50% compared with the UC-group (Fig. 2).

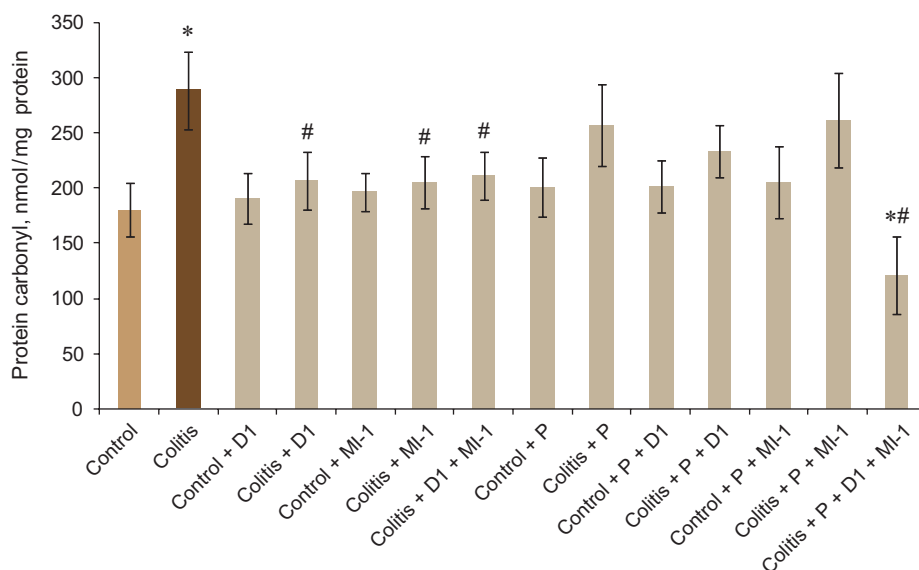


Fig. 1. The content of OMP in colonic mucosa of rats with UC treated with pyrrole derivatives (MI-1, D1) and prednisolone (P) ($M \pm m$; $n = 7$). * – $p \leq 0.05$ compared with control; # – $p \leq 0.05$ compared with the colitis group

Рис. 1. Вміст карбонільних груп білків у слизовій оболонці товстої кишки щурів після введення обох похідних піролу та преднізолону за виразкового коліту ($M \pm m$; $n = 7$). * – $p \leq 0,05$ порівняно з контролем; # – $p \leq 0,05$ порівняно з тваринами з експериментальним колітом

Since MI-1, D1 and prednisolone have restored the OMP content to the control values as well as TBA-active products content; we assume that these compounds could inhibit the processes of lipid and protein peroxidation and thus restore the prooxidant-oxidant balance.

At the next stage, we determined the activity of antioxidant defense enzymes – superoxide dismutase and catalase. It was found that in the UC-group SOD activity reduced by 27%, which could indicate SOD inhibition by excessive ROS [2]. Thus, due to the development of oxidative stress in animals with UC, there is an imbalance between the processes of lipid and protein oxidation and the antioxidant defense system activity, which is typical for chronic inflammatory processes including UC [17].

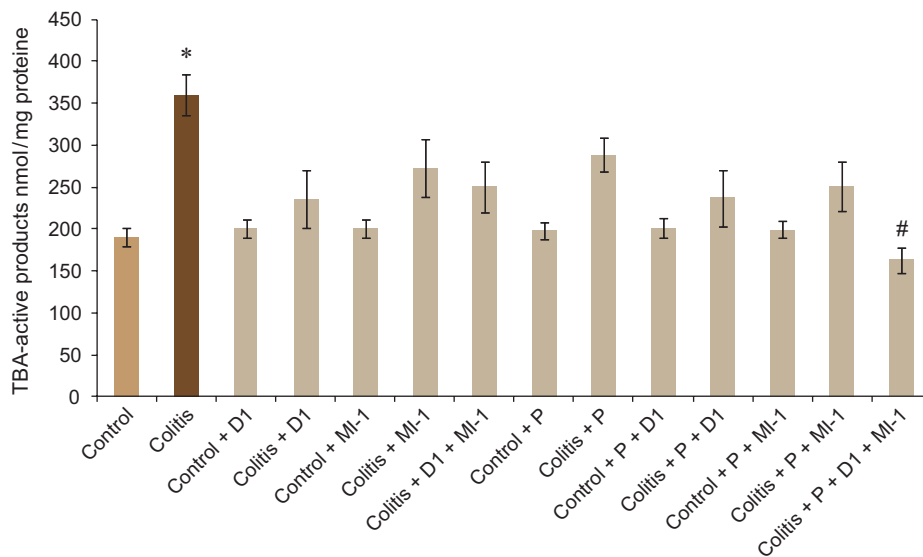


Fig. 2. The content of TBA-reactive substances in the colonic mucosa of rats with UC treated with pyrrole derivatives (MI-1, D1) and prednisolone (P) ($M \pm m$; $n = 7$). * – $p \leq 0.05$ compared with control; # – $p \leq 0.05$ compared with colitis

Рис. 2. Вміст ТБК-позитивних продуктів у слизовій оболонці товстої кишки щурів після введення обох похідних піролу та преднізолону за виразкового коліту ($M \pm m$; $n = 7$). * – $p \leq 0,05$ порівняно з контролем, # – $p \leq 0,05$ порівняно з колітом

Under the effect of all test compounds and their combinations except prednisolone + MI-1, SOD activity was restored to the control value, which could indicate this enzyme's activation and/or reduction of its functional load during the reduced ROS production. However, under the influence of MI-1 + P, SOD activity reduced to 45% (**Fig. 3**). The obtained results are consistent with our previous results [6, 8] according to which MI-1 administration led to 1.8-fold reduction in SOD activity. We supposed that the decreased SOD activity observed under the influence of MI-1 + P, apparently, is not due to the action of toxic peroxide products, as the content of TBARS and MPO did not change, but due to other factors. It is known that the expression of Cu/Zn-SOD at the oxidative stress is under the regulatory control of the signal PI3K/Akt kinase cascade, which, in turn, is closely related to the activation of a number of membrane kinase receptors, in particular insulin (INS-R) and insulin-like growth factor receptor (IGF1-R). According to our previous data, these activities could be blocked by micromolar concentrations of MI-1 [8, 14]. Such suppression of these receptors may be one of the reasons for the decrease in SOD activity under prolonged exposure to MI-1.

The absence of similar effects in other groups may be due to the combined effect of MI-1 and prednisolone on this enzyme. Thus, glucocorticoids have been found to inhibit SOD activity significantly [18]. Thus, their effect might be potentiated and, therefore, we observed SOD suppression.

Both pyrrole derivatives did not cause significant changes in catalase activity in our study (**Fig. 3**). However, there was an increase in this enzyme's activity by 20% compared with the control value in UC-rats that received prednisolone together with MI-1. This may be due to a negative feedback of SOD and catalase activities regulation due to the fact that hydrogen peroxide, which is a product of SOD, is a substrate for catalase [17]. Thus,

catalase is SOD antagonist in the cell and prevents the accumulation of the superoxide dismutase reaction product – hydrogen peroxide, which is an inhibitor of SOD, and a high degree of correlation between SOD and catalase activities has been established [17].

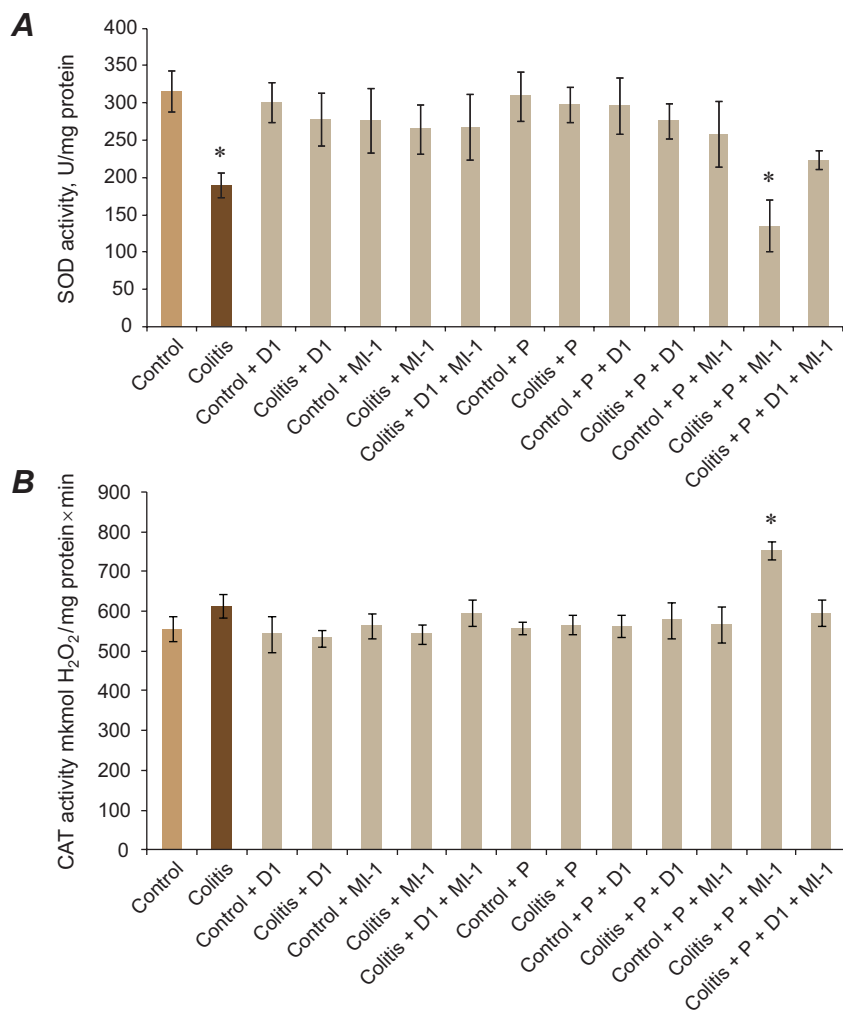


Fig. 3. Superoxide dismutase (SOD) (**A**) and catalase (CAT) (**B**) activities in the colonic mucosa of rats with UC treated with pyrrole derivatives (MI-1, D1) and prednisolone (P) ($M \pm m$; $n = 7$). * – $p \leq 0.05$ compared with control

Рис. 3. Активності супероксиддисмутази (SOD) (**A**) та каталази (CAT) (**B**) у слизовій оболонці товстої кишки щурів після введення обох похідних піролу і преднізолону за виразкового коліту ($M \pm m$; $n = 7$). * – $p \leq 0,05$ порівняно з контролем

Biochemical markers in blood serum of rats with UC treated with MI-1, D1 and prednisolone. The liver is an organ that first undergoes toxic effects of substances and plays a vital role in the intermediate metabolism, neutralization and excretion of those from the body [5, 6]. Highly sensitive indicators of liver damage and dysfunction are an increased activity of intracellular enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (ACT) in blood serum [3, 6]. Both enzymes enter the bloodstream

as a result of cell membrane damage and are well-known markers of liver (and some other internal organs) damage and indicators of the organism systemic condition.

It was found that blood serum ALT activity increased by 26%, which indicates some liver damage, and, consequently, the systemic colitis outcome in the body. However, blood serum AST did not change significantly.

After MI-1 treatment, ALT activity reduced by 23% compared with control and reduced by 38% compared with colitis, which could indicate the restoration of liver function. As expected, AST activity did not change. The de Ritis ratio was slightly increased in the experimental group (1.47 ± 0.15) compared with the control group (1.33 ± 0.13).

After D1 treatment, ALT activity also reduced by 39% compared with colitis, as in the previous group (**Fig. 4**). These changes could indicate the restoration of hepatocytes integrity and reduce the toxic load on the liver due to UC. AST activity did not change either. The observed decrease in blood serum ALT activity, in our opinion, may be due to the activation of the body's adaptive systems, stabilization of hepatocyte membranes, reduction of toxic products level in the blood and restoration of systemic redox state.

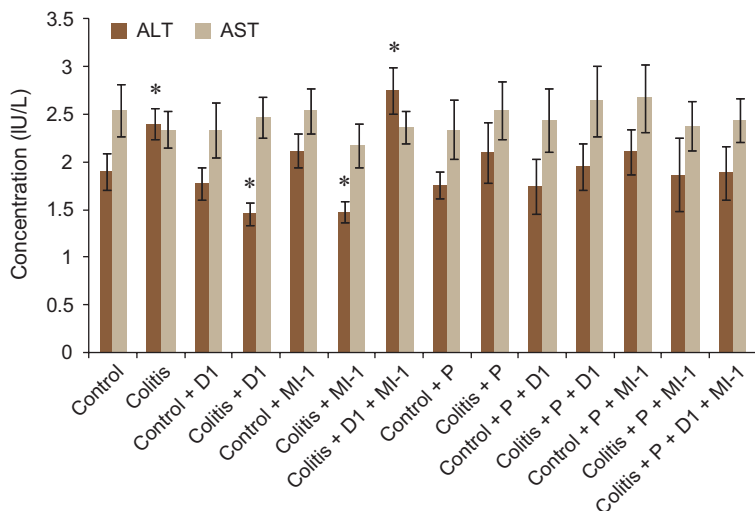


Fig. 4. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity in the serum of rats with UC treated with pyrrole derivatives (MI-1, D1) and prednisolone (P) ($M \pm m$; $n = 7$). * – $p \leq 0.05$ compared with the control

Рис. 4. Активність аланінамінотрансферази (ALT) і аспаратамінотрансферази (AST) у сироватці крові щурів після введення обох похідних піролу і преднізолону за виразкового коліту ($M \pm m$; $n = 7$). * – $p \leq 0,05$ порівняно з контролем

However, under the simultaneous influence of both compounds, ALT activity increased (by 44%), which is an indicator of hepatocyte damage, inflammatory processes in the liver; AST activity did not change either (**Fig. 4**). The de Ritis ratio decreased under the combined action of these compounds (0.86 ± 0.09), which indicates liver susceptibility to those compounds.

Increased serum bilirubin levels under pathology could indicate liver involvement, and may be due to an impaired liver bilirubin-secretory function on the background of toxic effects of substances, impaired bile flow to the intestine, impaired hepatic secretion of conjugated (direct) bilirubin into bile, and increased erythrocyte hemolysis. We observed that direct bilirubin in the colitis group increased by 48%, while total bilirubin was virtually

unchanged, indicating liver function deficiency and impaired formation and/or bile outflow (Fig. 5). This is a fairly common phenomenon under colitis [14]. The concentration of direct bilirubin under the influence of MI-1 did not change compared with control, but total bilirubin increased (by 38%) in this group. In the D1-treated UC-rats, changes in bilirubin content were similar – total bilirubin increased (by 51%) accompanied with no changes in the direct bilirubin content.

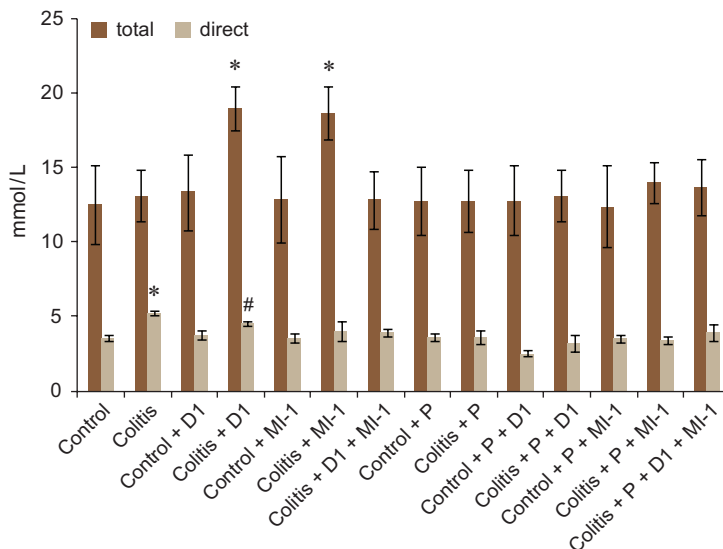


Fig. 5. The content of total and direct bilirubin in the blood serum of rats with UC treated with pyrrole derivatives (MI-1, D1) and prednisolone (P) ($M \pm m$; $n = 7$). * – $p \leq 0.05$ compared with colitis

Рис. 5. Вміст загального та прямого білірубину в сироватці крові щурів після введення обох похідних піролу і преднізолону за виразкового коліту ($M \pm m$; $n = 7$). * – $p \leq 0,05$ порівняно з контролем; # – $p \leq 0,05$ порівняно з колітом

Under the action of prednisolone, both alone and in combination with pyrrole derivatives, all tested blood serum parameters were restored to the control level, which may be due to complex anti-inflammatory and hepatoprotective effects of those.

Liver injury is a common concomitant pathology in IBD. The liver can suffer from the following reasons: due to the violation of the intestinal epithelium integrity and intestinal endotoxins entering the bloodstream. In addition, it can suffer from immune complexes as a product of the inflammatory process, which causes a functional load on the liver as a detoxification organ. With impaired absorption and digestion, the metabolism undergoes pathological changes, which is reflected in the liver as a digestive organ. Its functional overload could be due to the intensive metabolism of xenobiotics including drugs. For example, low molecule protein kinase inhibitors are metabolized predominantly in liver by Cyp3A4 cytochromes (in humans) or their analogues (rodents) [13]).

CONCLUSIONS

It has found that pyrrole derivatives used under chronic colitis could reduce the signs of inflammation, contribute to the normalization of colonic mucosa morphology, and redox balance (at the level comparable with that of reference drug prednisolone) which indicates their anti-inflammatory efficacy. However, they caused an increase in total bilirubin, which may be a sign of their adverse effects on the liver.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Human Rights: This article does not contain any studies with human subjects performed by any of the authors.

Animal studies: All international, national and institutional guidelines for the care and use of laboratory animals were followed.

AUTHOR CONTRIBUTIONS

Conceptualization, [R.V.K.]; methodology, [K.H.M.; R.V.K.; K.I.P.]; validation, [K.H.M.; R.V.K.]; formal analysis, [K.H.M.; R.V.K.]; investigation, [K.H.M.; R.V.K.; K.I.P.]; resources, [K.H.M.; R.V.K.; K.I.P.]; data curation, [K.H.M.; R.V.K.; K.I.P.]; writing – original draft preparation, [K.I.P.]; writing – review and editing, [K.H.M.]; visualization, [K.I.P.] supervision, [R.V.K.]; project administration, [R.V.K.]; funding acquisition, [-].

All authors have read and agreed to the published version of the manuscript.

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ВПЛИВ ПОХІДНИХ ПІРОЛУ НА ПРОЯВИ ЗАПАЛЕННЯ У ЩУРІВ ІЗ ХРОНІЧНИМ ВИРАЗКОВИМ КОЛІТОМ ЗА ЛІКУВАННЯ ПРЕДНІЗОЛОНОМ

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Вступ. У попередніх дослідженнях ми виявили протипухлинну та протизапальну активність інгібіторів протеїнкінази піролу – MI-1 (1-(4-Cl-бензил)-3-Cl-4-(CF₃-феніламіно)-1H-пірол-2,5-діон 1) і D1 (5-аміно-4-(1,3-бензотіазол-2-іл)-1-(3-метоксифеніл)-1,2-дигідро-3H-пірол-3-одина) у моделі раку товстої кишки щурів. Тому похідні піролу були спрямовані на виявлення у щурів протизапальної дії на моделі виразкового коліту, спричиненого оцтовою кислотою.

Матеріали та методи. Як препарат порівняння було використано преднізолон – протизапальний засіб глюкокортикоїдної природи, який вводили внутрішньо-очеревинно в дозі 0,7 мг/кг. Введення досліджуваних сполук здійснювали через 2 год після першого введення оцтової кислоти. Вміст білка в одержаних препаратах визначали за методом Лоурі та ін., 1951. Вміст малонового діальдегіду, карбонільних груп білків, а також активність ферментів антиоксидантного захисту як показники окислювально-відновного стану слизової оболонки товстої кишки вимірювали спектрофотометрично. Статистичний аналіз отриманих результатів проводили за допомогою програми MS Excel-2013.

Результати. За хронічного коліту в слизовій оболонці товстої кишки збільшується кількість карбонільних груп і продуктів перекисного окиснення ліпідів, що підтверджує розвиток окисного стресу. Введення похідних піролу поокремо сприяє наближенню цих показників до норми. У разі додавання преднізолону такий ефект не спостерігали. За коліту встановлено зменшення активності супероксиддисмутази, що є типовим явищем для хронічного запалення і вказує на виснаження ферменту.

За коліту активність аланінамінотрансферази і вміст прямого білірубину зростають, що вказує на функціональне навантаження на печінку і є системними проявами запалення товстої кишки. Похідні піролу сприяють зменшенню цього навантаження, що свідчить про відновлення до норми активності аланінамінотрансферази і вмісту прямого білірубину.

Висновки. Встановлено, що похідні піролу під час застосування за хронічного коліту зменшують прояви запалення, сприяють наближенню до норми структури слизової оболонки (на рівні препарату порівняння преднізолону), що доводить їхню протизапальну ефективність, однак зумовлюють зростання рівня загального білірубину, що може бути ознакою негативного впливу на печінку.

Ключові слова: експериментальний коліт, преднізолон, похідне піролу, слизова оболонка ободової кишки