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## STUDY OF THE ANTIULCER ACTIVITY OF GARDEN CABBAGE EXTRACT ON THE CHRONIC ACETIC ULCER MODEL IN RATS

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*The aim of the study was to study the gastroprotective properties of the dry extract of garden cabbage in the model of chronic acetic ulcer in rats.*

**Materials and methods.** Chronic ulcerative lesions of the gastric mucosa of rats were modeled by introducing 0.05 ml of a 30 % solution of acetic acid into the subserous layer of the stomach wall. The dry extract of garden cabbage in a conditionally therapeutic dose of 50 mg/kg and reference drugs omeprazole and altan were administered intragastrically for 10 days, starting from the second day of the experiment. When choosing the duration of the course of treatment, we proceeded from the data that the effectiveness of the antiulcer action in the clinic is assessed after 10-12 days of treatment. The percentage of animals with ulcers in the group, the state of the gastric mucosa were evaluated, the ulcer index and antiulcer activity were calculated. To elucidate the possible mechanism of action of the extract, we studied its effect on synthetic processes in terms of the content of RNA and DNA in homogenates of the gastric mucosa by the spectrophotometric method by reaction with perchloric acid.

**Results.** On the model of stomach damage, caused by acetic acid, a pronounced antiulcer activity of the extract (54.26) was established at the level of omeprazole (54.62). The maximum antiulcer activity (72.75) was revealed when using the combination of the extract with omeprazole, which, in terms of ulcerative effect, is superior to monotherapy with the extract, omeprazole and altan (35.08).

Reparative regeneration is a component of an adaptive tissue reaction; under conditions of violation of the reparative potencies of the mucosa, chronic diseases of the gastrointestinal tract develop. Since the final goal of antiulcer therapy is the healing of the ulcer, and the basis of this process is reparative regeneration, the reparative properties of the extract have been studied. Under the influence of cabbage extract, the content of RNA and DNA in the mucosa probably increased by 2.8 and 2.4 times, respectively, at the same level with omeprazole. If possible, to activate the synthetic processes of DEGC and omeprazole, altan significantly prevailed.

The most pronounced effect of enhancing reparative processes was established with the combined use of the extract and omeprazole, which turned out to be a significant increase in the content of RNA and DNA in the gastric mucosa by 3.2 and 2.9 times compared with the control.

**Conclusions.** On the model of chronic damage to the stomach of rats, cabbage extract showed an antiulcer effect, the severity of which was not inferior to the comparison drug, the proton pump inhibitor omeprazole, and significantly exceeded the phytopreparation - altan. The combined use of the extract and omeprazole showed the highest preventive effect of preventing the negative effects of acetic acid on the gastric mucosa. One of the mechanisms of the gastroprotective action of the extract is its ability to enhance reparative processes in the gastric mucosa. The results obtained indicate the prospects for further research on the antiulcer properties of cabbage extract with a view to its use in the complex therapy of peptic ulcer

**Keywords:** cabbage, extract, antiulcer activity, omeprazole, gastroprotective properties, reparation

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### 1. Introduction

To date, peptic ulcer is about 36 % of the pathologies of the gastrointestinal tract. The highest frequency of its distribution falls on highly developed countries. In Western European countries, 10–15 % of men and 4–15 % of women suffer from peptic ulcer during their lifetime. More often this pathology occurs in people of young, working age (20–40 years). Peptic ulcer in childhood and adolescence is no longer considered a rare disease and today is a serious problem in pediatrics [1]. These facts testify to the socio-economic significance of solving this medical problem.

The market for drugs with proven antiulcer activity today exceeds 500 items, while the problem of effective therapy is far from being solved. Despite the use of sufficiently active preventive measures and constantly improving methods of treatment (there are more than 1000 of them), even with the complex use of highly effective antiulcer drugs, relapses are observed in 30–82 %, complicated forms of peptic ulcer occur in 26–42 % of cases, and in 15–25 % of patients there is a problem of resistance of gastroduodenal ulcers to modern therapeutic effects [2].

In addition, it should be emphasized, that in almost a third of patients taking drugs is accompanied by the manifestation of one or another side effect, the development of pseudomembranous colitis, intestinal dysbacteriosis, and 5–10 % of the population is allergic to antibiotics. Stopping the use of selective agents leads to secretory recoil (withdrawal syndrome, "rebound"), which can provoke a relapse of the disease. There is a risk of the formation of antibodies to H<sub>2</sub>-histamine blockers as a result of their long-term use. Pharmacogenic anacidity promotes bacterial proliferation and increases the level of nitrosamines, which can provoke carcinogenesis.

Therapy of peptic ulcer cannot be limited only to anti-*Helicobacter pylori* regimens, no matter how perfect they are. Undoubtedly, the treatment should be multi-component with the inclusion of active drugs that affect the "host factor" and the restoration of trophic processes in the gastric mucosa (GM) and duodenum, which leads to recovery [3].

In recent years, pharmacologists have made certain attempts to develop a complex drug with a diverse effect for the treatment of chronic gastroduodenal ulcers. The problem of systemic effects on the patient's body in the form of monotherapy or as one of the components of a complex of therapeutic measures can be solved by phytotherapy [4]. The undoubted advantage of phytopreparations is a wide range of their biological effects, low toxicity or lack thereof, mildness of action, interchangeability of plants. Means of plant origin can be used at the initial stages of peptic ulcer, in the period of exacerbation – as an additional treatment in combination with potent substances, and at the stage of anti-relapse therapy, a departure from the xenobiotic load may well be justified. It is difficult to overestimate the importance of plant preparations during periods of remission or stabilization of the pathological process, when they act as supportive ones, preventing exacerbations. Taking into account the effectiveness, tolerability and cost-effectiveness, phytotherapeutic drugs are not competing, but complementary to modern pharmacotherapy for the treatment of gastric and duodenal ulcers [5, 6].

In official medicine, the registry of antiulcer drugs from plants, the effectiveness of which has been confirmed by experimental and clinical studies, is very limited [7]. The data of traditional medicine on the gastroprotective properties of plant sources gives experimenters ample opportunities to create new drugs that have not yet found application in the practice of treating patients with gastric and duodenal ulcers. Historically formed in folk and traditional medicine, approaches to the treatment of gastric ulcer with herbal preparations for the prevention and increase in the inter-relapse period have found a new impetus due to original technologies for obtaining new remedies from plant materials. One of the promising areas is the study of drugs, derived from biologically active substances of garden cabbage, widely used in folk medicine for the prevention and treatment of cancer, cardiovascular diseases, nervous disorders, diseases of the gastrointestinal tract, metabolic disorders, gout, etc. The presence of a combination of biologically active substances (flavonoids, organic acids, polysaccharides, sulfur-containing glycosides – glycobrasidin, neoglycobrasidin, vitamins C, P, PP, B<sub>1</sub>, B<sub>2</sub>, B<sub>6</sub>, K, D, E and

U, carotene, pantothenic and folic, calcium, sodium, magnesium, phosphorus, etc.) in this plant causes a large number of its pharmacological effects: anti-inflammatory, antioxidant, membrane stabilizing, reparative and antimicrobial [8–10]. An analysis of modern scientific literature data showed that there are no drugs and dietary supplements containing raw cabbage in the world, which makes it promising to create a domestic gastroprotective drug from cabbage, widely cultivated in Ukraine. Therefore, the study of the gastroprotective properties of biologically active substances of garden cabbage, which has a rich raw material base for the creation of a promising domestically produced antiulcer agent for pathological conditions of the stomach, is relevant within the framework of the drug import substitution program.

The purpose of this work was to study the gastroprotective properties of the dry extract of garden cabbage on the model of experimental lesions of the gastric mucosa with hydrochloric acid.

## 2. Materials and methods

The study was performed on nonlinear white rats of both sexes weighing 180–220 g, which were kept in standard conditions of vivarium of National University of Pharmacy. The study is a fragment of the research work of the National University of Pharmacy on the problem of the Ministry of Health of Ukraine "Pharmacological study of biologically active substances and medicinal products" and conducted during 2020–2021.

The subject of the study was a dry extract of 1:5 alcohol from cabbage leaves (DECG), obtained at the Department of Chemistry of Natural Compounds of the National University of Pharmacy. The substance was isolated from the aerial part (leaves) of white cabbage *BRASSICAE oleraceae* convar. *capitatae* var. *albae* by extracting it with 10 ml of 50 % ethanol, followed by evaporation and drying.

Chronic gastric ulcer was reproduced by Takagi et al. in the modification of A.A. Nikulin and S.I. Budantseva [11]. Chronic damage to the GM was reproduced on 48 nonlinear white rats under inhalation anesthesia after a 24-hour fast without limiting the drinking regimen. The animals underwent laparotomy and injection of 0.05 ml of a 30 % solution of acetic acid into the subserous layer of the stomach wall [11]. This model was chosen taking into account its high reproducibility and compliance with gastric ulcer in humans. All layers of the gastric wall are involved in the ulcerative process, exudation and leukocyte infiltration of the mucous, submucosal and muscular layers of the stomach around the ulcer are noted.

Animals were kept under standard vivarium conditions: at a temperature of 20–22 °C, humidity not more than 60–70 %, air exchange volume (exhaust-tide) 8/10, day/night light regimen in standard aluminum cages, no more than 5 animals in each. The work with animals was carried out in accordance with the "General ethical principles of animal experiments" (Ukraine, 2001), which is consistent with the provisions of the "European Convention for the Protection of Laboratory Animals Used for Scientific Purposes" (Strasbourg, 1986), Law of Ukraine No. 3447-IV dated February 21, 2006 "On the Protection

of Animals” No. 249 of 01.03.2012 “The Procedure for Conducting Experiments on Animals by Scientific Institutions”.

The Commission on Bioethics of the National University of Pharmacy did not reveal any violations of moral standards during the planning and conduct of the study (protocol No. 4 dated 02.10.2020). All pain manipulations were performed under etaminal sodium anesthesia (40 mg/kg intraperitoneally). Euthanasia was performed by an overdose of ether anesthesia or cervical dislocation. The Commission on Bioethics of the National University of Pharmacy found no violations of moral and ethical standards in the planning and conduct of research work.

The test animals were divided into 6 groups of 8 animals each: group 1 – intact control (animals that received the solvent – purified water); group 2 – control pathology – animals with simulated ulcerative damage; 3–6 – animals that were injected with DEGC at a dose of 50 mg/kg against the background of model pathology; omeprazole at a dose of 2,5 mg/kg; DEGC at a dose of 50 mg/kg together with omeprazole at a dose of 2,5 mg/kg; altan at a dose of 1 mg/kg. The drugs were administered intragastrically for 10 days, starting from the second day of the experiment. When choosing the duration of the course of treatment, we proceeded from the data that the effectiveness of the antiulcer action in the clinic is assessed after 10-12 days of treatment. Treatment is considered effective if the size of the ulcer during this period is reduced by 2 times.

After 10 days, the animals were decapitated and the state of the gastric mucosa was studied. The assessment of the intensity of ulcerative lesions and the antiulcer activity of the extract was carried out according to macroscopic indicators of the intensity of the formation of ulcerative defects in the GM: the percentage of animals with ulcers in the group ( $A_{ulc}$ ), the average area of ulcers in the group ( $S_{ulc}$ ), mm<sup>2</sup>, ulcerative index (UI), antiulcer activity (AA, %).

The ulcerative index and antiulcer activity were calculated using the formulas:

$$UI = (S_{ulc} \times A_{ulc}) / 100,$$

$$AA, \% = 100 \% - ((UI_{tr} \times 100 \%) / UI_c),$$

where  $UI_{tr}$  – UI in the group of animals with control pathology, which were treated;

$UI_c$  – UI in the group of animals with control pathology (untreated).

To elucidate the possible mechanism of the action of DEGC, its effect on synthetic processes was studied by the content of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) in homogenates of the gastric mucosa by the spectrophotometric method by reaction with perchloric acid.

The concentration of DNA and RNA was calculated using the formulas:

$$C_{DNA} = ((E_{270} - E_{290}) : 0.19) \times 10.1,$$

$$C_{RNA} = ((E_{270} - E_{290}) : 0.19) \times 10.5,$$

where  $E_{270}$ ,  $E_{290}$  is the optical density of the samples, determined on the SF-46 spectrophotometer in ultraviolet light at 270 and 290 nm in cuvettes 10 mm thick.

To obtain the statistical analyses, use analysis of variance (Kruskal-Wallis test), when comparing samples – U-Mann-Whitney test at probability level  $p \leq 0.05$ . Statistical data processing was performed using software package "STATISTICA for WINDOWS 6.0" [12, 13].

### 3. Research results

A gastric ulcer with acetic acid damage developed after 48 hours and was a large crater-like lesion with a granulation rampart around the perimeter that did not heal for a long time.

In experimental chronic acetate ulcer in all rats of the control group on the 10th day of the experiment, swelling, hyperemia of the GM, gastric distension, impaired folding, small erosions and one deep ulcer with severe inflammation in the periulcerous zone, the diameter of which reached, were observed macroscopically. Penetration of the ulcer into the liver was found in two animals, which indicates the severity of the reproduced pathological process. The average area of ulcerative defects was  $24.66 \pm 3.20$  mm<sup>2</sup>, UI – 24.66 (Table 1).

The introduction of DEGC contributed to a decrease in the severity of the course of the pathological process, which was characterized by the restoration of GM wrinkling and its color to the level of intact animals, but gastric distention persisted. DEGC significantly reduced the average area of ulcerative defects compared to the control group by 2.2 times, its UI and antiulcer activity were 11.28 and 54.26 %, respectively (Table 1).

In the group of animals, treated with the reference drug omeprazole, there was a decrease in appetite compared with other test groups, which may be due to its antisecretory effect. Macroscopically, the GM was characterized by moderate hyperemia and impaired folding. Along with this, under the influence of omeprazole, a decrease in the size of ulcers was noted compared to the control group, similar to the effect of DEGC, by 2.4 times, the antiulcer activity was 54.62 % (Table 1). Therefore, the analysis of the obtained data showed that the ulcerative healing effect, revealed with the use of DEGC, was equivalent to the effect of the proton pump inhibitor omeprazole. Against the background of the use of the herbal antiulcer agent altan, pronounced hyperemia and swelling of the buccal, changes in its folding and swelling persisted. Altan had a weak antiulcer effect at the level of 35.08 %, in terms of efficiency it was significantly inferior to the studied extract and omeprazole by 1.4 times (Table 1).

To elucidate the possible mechanism of the action of DEGC, its effect on synthetic processes in terms of the content of RNA and DNA in homogenates of the gastric mucosa was studied by the spectrophotometric method by reaction with perchloric acid [14].

Reparative regeneration is a component of an adaptive tissue reaction; under conditions of violation of the reparative potencies of the mucosa, chronic diseases of the gastrointestinal tract develop. Since the final goal of antiulcer therapy is the healing of the ulcer, and the basis of this process is reparative regeneration, it was of interest to study the reparative properties of the extract.

In our experiment, the effect of the extract and reference drugs on synthetic processes under conditions of ulcerative lesions was determined by the content of RNA and DNA in the gastric mucosa.

As the study showed, the content of nucleic acids in the mucosal homogenate of animals in the control pathology group probably decreased compared to intact animals (Table 2).

Table 1

Influence of DEGC on the condition of the gastric mucosa of rats with experimental gastric ulcer caused by acetic acid ( $X \pm Sx$ , n=8)

Experience conditions	Animals with ulcers, %	Mean ulcer area, mm <sup>2</sup>	UI, c.u.	AA, %
Intact control	0	0	–	–
Control	100	24.66±3.20*	24.66	–
DEGC, 50 mg/kg	100	11.28±1.12**/a/#	11.28	54.26
Omeprazole, 2.5 mg/kg	100	11.19±1.56**/a/#	11.19	54.62
Altan, 1 mg/kg	100	16.01±1.60**/#	16.01	35.08
DEGC, 50 mg/kg + Omeprazole, 2.5 mg/kg	100	6.72±1.07**/a	6.72	72.75

Note: \* – differences are statistically significant relative to the values of the intact control,  $p < 0.05$ ; \*\* – differences are statistically significant relative to the control values,  $p < 0.05$ ; a – differences are statistically significant relative to the values of altan,  $p < 0.05$ ; # – differences are statistically significant relative to the values of DEGC + omeprazole,  $p < 0.05$

All the studied drugs probably activated reparative processes at the intracellular level, which was manifested by an increase in the level of RNA and DNA com-

pared with the control pathology and intact control, except for the reference drug altan, against which there was a significant increase only in the RNA content (Table 2).

Table 2

Effect of DEGC on nucleic acid metabolism in experimental gastric ulcer caused by acetic acid ( $X \pm Sx$ , n=8)

Experience conditions	The content of nucleic acids in the homogenate of the gastric mucosa, µg/ml	
	RNA	DNA
Intact control	4.15±0.23	1.67±0.07
Control	2.14±0.16*	0.52±0.09*
DEGC, 50 mg/kg	5.97±0.16**/a/#	1.26±0.10**/a
Omeprazole, 2.5 mg/kg	5.35±0.15**/a/#	1.37±0.08**/a
Altan, 1 mg/kg	3.43±0.19**/#	0.74±0.07#
DEGC, 50 mg/kg + Omeprazole, 2.5 mg/kg	6.78±0.18**/a	1.49±0.09**/a

Note: \* – differences are statistically significant relative to the values of the intact control,  $p < 0.05$ ; \*\* – differences are statistically significant relative to the control values,  $p < 0.05$ ; a – differences are statistically significant relative to the values of altan,  $p < 0.05$ ; # – differences are statistically significant relative to the values of DEGC + omeprazole,  $p < 0.05$

The obtained results are consistent with the literature data on the proliferation of cells in the area of the edges of the ulcer and increased synthesis of nucleic acids during the healing of ulcerative lesions of the gastric mucosa.

Under the influence of the studied extract, the content of RNA and DNA in the mucosa probably increased by 2.8 and 2.4 times, respectively, at the same level as the proton pump inhibitor omeprazole. If possible, to activate the synthetic processes, the extract and omeprazole significantly exceeded the herbal antiulcer drug altan.

#### 4. Discussion of research results

It should be noted, that the most common means of treating pathologies of the stomach and duodenum are antacids and antisecretory agents, which

include selective and non-selective anticholinergics, histamine H<sub>2</sub>-receptor antagonists and proton pump inhibitors [15]. The latter, in addition to reducing the aggressive properties of gastric juice, do not have a probably proven ability to stimulate the protective mechanisms of the mucous membrane, and long-term treatment with these drugs is associated with side effects and poor healing of ulcers, which leads to their recurrence.

The nomenclature of gastroprotectors, which include reparants, cytoprotectors and antioxidants, is represented by several drugs, their use is also limited by adverse reactions [16, 17].

Therefore, in the absence of Helicobacter pylori infection in peptic ulcer disease, it is advisable to combine the above drugs and natural products, which, due to their multicomponent composition, have an antiulcer ef-

fect, affecting various mechanisms of mucosal integrity violation.

In our experiment, combined treatment with the extract and omeprazole for 10 days led to a significant decrease in the average area of ulcerative defects by 3.7 times compared with the control. The studied combination of drugs was 34 % and 33 % more active than the extract and omeprazole, respectively, and 107 % more effective than the reference drug altan. The advantages of combined therapy were also evidenced by such macroscopic signs as the absence of swelling and hyperemia, normal folding of the mucous membrane.

The most pronounced effect of enhancing reparative processes was established with the combined use of the extract and omeprazole, which was manifested by a significant increase in the content of RNA and DNA in the gastric mucosa by 3.2 and 2.9 times, respectively. The indicated combination in terms of increasing the level of RNA exceeded the extract, omeprazole and altan by 13.6 %, 26.7 % and 97.7 %, respectively, and was more effective than the studied agents in increasing DNA - by 18.3 %, 8.8 % and 101.4 % respectively.

**Study limitation.** The study is limited to a macroscopic study of the effect of the extract on the state of the gastric mucosa, which opens up the prospect of further histological studies to investigate the gastroprotective activity of the studied extract.

**The prospect of further research** is to study the mechanisms of the gastroprotective action of cabbage extract on models of acute and subacute ulcer lesions.

## 5. Conclusions

1. On the model of chronic lesions of the gastric mucosa, the pronounced antiulcer activity of cabbage extract (54.26 %) was established at the level of omeprazole. The maximum antiulcer activity was established when using the combination of the extract with omeprazole, which, in terms of antiulcer effect, is superior to monotherapy with the extract, omeprazole and altan.

2. The mechanism of the antiulcer action of cabbage extract is to enhance the reparative processes in the mucous membrane: the content of RNA and DNA significantly increased by 2.8 and 2.4 times, respectively, at the same level with omeprazole.

3. According to the ability to activate synthetic processes, the studied extract and omeprazole significantly exceeded the herbal antiulcer drug altan.

## Conflict of interests

The authors declare that they have no conflict of interest regarding this research, including financial, personal, authorship or any other kind of conflict that could influence the research and its results, presented in this article.

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## Data Availability

The data will be provided upon a reasonable request.

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