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STUDY OF THE ANTIULCER ACTIVITY OF DRY EXTRACT OF GARDEN CABBAGE ON A MODEL OF SUBCHRONIC GASTRIC ULCER

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Мета – *вивчення гастропротекторних властивостей сухого екстракту капусти городньої на моделі експериментального ураження слизової оболонки шлунка ацетилсаліциловою кислотою.*
Матеріали і методи. *Субхронічне виразкове ураження слизової оболонки шлунка щурів моделювали внутрішньошлунковим уведенням ацетилсаліцилової кислоти у дозі 150 мг/кг протягом 3-х днів. Сухий екстракт капусти городньої в умовнотерапевтичній дозі 50 мг/кг і препарати порівняння омепразол та альтан уводили щодня під час відтворення патології та ще протягом 2 днів. Оцінювали відсоток тварин з виразками у групі, стан слизової оболонки шлунка, розраховували виразковий індекс та противиразкову активність. Гістологічно досліджували потужність мукоїдної секреції слизоутворюючими клітинами покривно-ямкового епітелію поза зон деструкцій за виразністю ШІК-реакції.*
Результати. *Встановлено, що сухий екстракт капусти городньої у дозі 50 мг/кг нівелював ульцерогенну дію ацетилсаліцилової кислоти на рівні омепразолу, що відображувалося зменшенням виразкового індексу в 3,3 рази, його противиразкова активність склала 83 %. Максимальний противиразковий ефект показала комбінація сухого екстракту капусти городньої з омепразолом, яка достовірно зменшувала ризик розвитку пошкоджень слизової оболонки шлунка, за виразковим індексом перевершувала монотерапію сухим екстрактом капусти городньої, омепразолом та альтаном, противиразкова активність була на рівні 94 %. Сухий екстракт капусти городньої стабілізував процеси мукоїдного синтезу, при його поєднанні з омепразолом інтенсивність ШІК-реакції поверхнево-ямкового епітелію слизової оболонки на всіх досліджених ділянках не відрізнялася від інтактного контролю. Отримані дані дозволяють вважати сухий екстракт капусти городньої гастропротектором.*
Висновки. *На моделі ураження шлунка щурів ацетилсаліциловою кислотою сухий екстракт капусти городньої виявив противиразкову дію, за виразністю якої не поступався препарату порівняння інгібітору протонної помпи омепразолу та значно перевершував фітозасіб таблетки альтану. Комбіноване застосування сухого екстракту капусти городньої та омепразолу показало найвищий профілактичний ефект щодо негативного впливу НПЗП на слизову оболонку шлунка. Одним із механізмів гастропротекторної дії сухого екстракту капусти городньої є його здатність посилювати слизоутворення клітинами покривно-ямкового епітелію шлунка. Отримані результати свідчать про перспективність подальшого дослідження противиразкових властивостей сухого екстракту капусти городньої з метою його застосування в комплексній терапії виразкової хвороби та профілактиці НПЗП-гастропатій.*
Ключові слова: *виразкова хвороба, ацетилсаліцилова виразка, сухий екстракт капусти городньої, противиразкова активність*

1. Introduction

Peptic ulcer and duodenal ulcer is one of the central problems of modern gastroenterology. In recent years, the frequency of peptic ulcer averages at 10 % and there is no tendency to its reduction. High incidence, frequent relapses, long-term disability of patients, significant economic losses – all this allows us to attribute the problem of peptic ulcer to the number of the most relevant in modern medicine.

Currently, the imbalance between the factors of aggression and protection of the mucous membrane of the stomach and duodenum is of great importance in the formation of ulcerative lesions [1]. It should be noted that non-steroidal anti-inflammatory drugs, which are now widely used in patients with cardiovascular, inflammatory, and degenerative-dystrophic diseases of the musculoskeletal system, are factors that damage mucous membranes [2]. Peptic ulcers of the stomach are associated with the ability of nonsteroidal anti-inflammatory drugs to suppress the activity of cyclooxygenase-1, resulting in blocking the synthesis of prostaglandins by the mucous membrane, the main physiological effects of which are to stimulate the secretion of protective bicarbonates and mucus, regulate regeneration and enhance local blood flow [3].

Despite a fairly wide arsenal of modern antiulcer drugs (H. pylori remedies, proton pump inhibitors, H_2 blockers, antacids, antispasmodics, drugs with cytopro-

tective and reparative properties: bismuth subcitrate, sucralfate, misoprostol) the problem of effective prevention and occurrence of peptic ulcer and its treatment remains unsolved [4, 5].

One of the most promising ways of eliminating adverse ulcerogenic action of nonsteroidal anti-inflammatory drugs and treatment of ulcerative lesions of different etiopathogenesis is the use of drugs of plant origin, which have a wide range of pharmacological actions on the background of low toxicity, they can be administered in monotherapy and in combination with anti-ulcer remedies [6, 7].

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

2. Planning (methodology) of research

The subject of research was dry extract produced from garden cabbage at the Department of pharmacognosy of National University of Pharmacy.

The garden cabbage (Brassica oleracea L.) is widely used worldwide as a vegetable crop, traditional medicine has used it in the treatment of various diseases, including the gastrointestinal tract. Scientific publications in recent years have demonstrated the presence of cabbage pharmacological properties caused by the complex of biologically active compounds in its composition, which was the justification an experimental study of the dry extract produced from cabbage garden [8–10].

Previously conducted studies have shown a pronounced gastroprotective effect of dry extract of garden cabbage in acute alcohol-prednisolone gastric ulcer [11, 12], which suggests antiulcer effect of herbal remedy in an experimental model of subchronic ulcerative lesions of the stomach.

3. 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.

When working with animals, they adhered to the International Code of Medical Ethics (Venice, 1983), the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986), the "General Ethical Principles for Animal Experiments" adopted by the First National Congress on bioethics (Kiev, 2001), Directive 2010/63/EU of the European Parliament and the Council on the protection of animals used for scientific purposes and the Law of Ukraine "On the Protection of Animals from Cruelty" N 3477-IV of 21.02.2006. Euthanasia was performed by decapitation with mild inhalation anesthesia.

Experimental lesions of the mucous membrane of the stomach was simulated by 5-fold introduction of acetylsalicylic acid (acetylsalicylic acid-Darnitsa, pills, 500 mg, «Pharmaceutical Firm «Darnitsa», Ukraine) for 3 days intragastric dose of 150 mg/kg [13].

Dry extract of garden cabbage in dose of 50 mg/kg and the drugs of comparison were administered simultaneously with acetylsalicylic acid intragastrically 1 time a day for 5 days starting from the day of introduction of the ulcerogenic agent.

The study was carried out in comparison with domestic anti-ulcer herbal remedies Altan (Altan, pills, 10 mg, PAO NPC «Borschagovsky CPP», Ukraine) at a dose of 1 mg/kg and antisecretory agents from the group of proton pump inhibitors –omeprazole (Omez capsules, 20 mg, «Dr. Reddy's Laboratories Ltd», India) at a dose of 2.5 mg/kg, which is widely used in the treatment of peptic ulcer disease. Dose regimen comparison were calculated using conversion factor [14].

Experimental animals were divided into 6 groups of 8 animals each: group

1 – intact control;

2 – control pathology of animals, which was modeled ulcerative damage acetylsalicylic acid;

3 – animals, which on the background of the model pathology were administered a dry extract of cabbage at a dose of 50 mg/kg;

4 – animals, which on the background of the model pathology was administered omeprazole at a dose of 2,5 mg/kg;

5 – animals, which on the background of the model pathology were administered a dry extract of cabbage at a dose of 50 mg/kg and omeprazole at a dose of 2,5 mg/kg;

6 – animals, which on the background of the model pathology have introduced pills Altan at a dose of 1 mg/kg.

On the 5th day animals of all groups were withdrawn from the experiment, removed the stomach, cut him open along the lesser curvature, washed with saline and performed macro- and microscopic examination.

The degree of damage of the gastric mucosa was evaluated in points:

0 points – no visible damage;

1 point – the presence of edema, hyperemia, hemorrhages, 1 to 3 small ulcers;

2 points – few small ulcers (more than 3) or 1 ulcer of considerable size;

3 points – an ulcer of considerable size (diameter up to 4 mm) and several small ulcers;

4 points – multiple large ulcers;

5 points – a perforated ulcer.

In each group, the ulcer index was calculated using the formula:

Ulcer index = (arithmetic mean state of the mucous membrane in the group, points x animals with ulcers in the group, %)/100

Antiulcer activity was calculated by the formula [13]:

Antiulcer activity, %=100 %–((ulcer index in the experimental group x 100 %)/ulcer index in the control group).

Histological examinations were subjected to mucosa fondling, prepyloric and pyloric divisions of the stomach. For the assessment of the protective mucus barrier performed the reaction by Mac-Manus (detection of neutral mucopolysaccharides) [15, 16].

Power mucoid secretion of slime by the cells of the cover-pit epithelium outside the areas of degradation was assessed by expression of PAS-reaction: 0 – no staining; score 1 – weak staining, 2 points – moderate staining; 3 points – an expressive color.

Microscopic study of micro specimens performed under a Granum microscope, microphotography, microscopic images was performed with a digital camcorder Granum DCM 310. The photographs were processed on a computer Pentium 2,4 GHz using the program Toup View. To obtain the statistical analyses used analysis of variance (test Kruskal-Walis), when comparing samples – U-Mann-Whitney test at probability level $p \leq 0.05$ [17, 18]. Statistical data processing was performed using software package "STATISTICA for WINDOWS 6.0".

4. The results of the study

A macroscopic study of the gastric mucosa of intact rats was unchanged, in the control pathology group, on the background of acetylsalicylic acid administration, in 100 % of the animals, mucosal lesions were observed, which were characterized by edema, hyperemia, large hemorrhagic erosions and ulcers of irregular shape. The ulcer index was 3.63 points (Table 1). The introduction of dry cabbage extract at a dose of 50 mg/kg eliminated the ulcerogenic effect of acid and increased the reparative processes in 50 % of rats, which was reflected by a decrease in the degree of mucosal lesion, the ulcer index was 0.6. A similar result was obtained when studying the effect of the comparison drug omeprazole, which showed a similar gastroprotective effect (Table 1).

Table 1

The effect of dry extract of garden cabbage on the state of the mucous membrane stomach rats in terms of experimental lesions of the stomach caused by acetylsalicylic acid (n=8)

Groups of rats	Condition of the gastric mucosa			
	% of animals with ulcers	Condition of the gastric mucosa, points	Ulcer index, points	Antiulcer activity, %
Intact control (IC)	0 (0/8)	0±0	0	-
Control pathology (CP)	100 (8/8)	3.63±0.26*	3.63	-
Cabbage extract, 50 mg/kg	50 (4/8)	1.1±0.44**	0.6	83
Omeprazole, 2,5 mg/kg	50 (4/8)	1.3±0.49**	0.7	81
Cabbage extract, 50 mg/kg + Omeprazole, 2,5 mg/kg	37.5 (3/8)	0.5±0.27**/Ω/#/Ψ	0.2	94
Altan, 1 mg/kg	62.5 (5/8)	1.63±0.50**/Ω	1.0	72

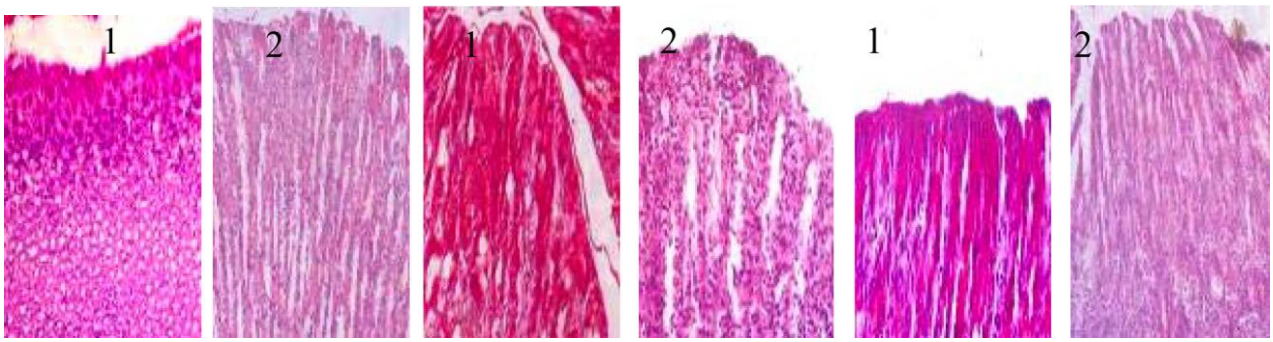
*Nots: * – differences are statistically significant with respect to group IC, $p<0.05$; ** – differences are statistically significant with respect to group CP, $p<0.05$; Ω – differences are statistically significant with respect to group altan, $p<0.05$; # – differences are statistically significant with respect to group cabbage extract, $p<0.05$; ψ – differences are statistically significant with respect to group omeprazole, $p<0.05$*

The comparison drug altan showed significantly lower anti-ulcer activity, however, the differences between it and omeprazole had only a tendency character (Table 1).

Maximum antiulcer activity shows a combination of a dry extract of cabbage with omeprazole which significantly reduces the risk of damage to the mucous membrane of the stomach and superior to monotherapy extract, omeprazole and altan.

The degree of damage in animals with visible changes in the state of the mucous membrane of the stomach (37.5 %) (Table 1) was characterized in 2 rats with slight edema, hyperemia, and only in one rat 4 small ulcers were revealed.

When setting a PAS-reaction on histological sections fundus part intact animals in the apical parts of the cells of the surface epithelium, the cytoplasm of cells pit epithelium and mucous cells of the glandular tubes was discovered a significant amount of neutral mucopolysaccharides (Fig. 1, *a*).



a *b* *c* *d* *e* *f*

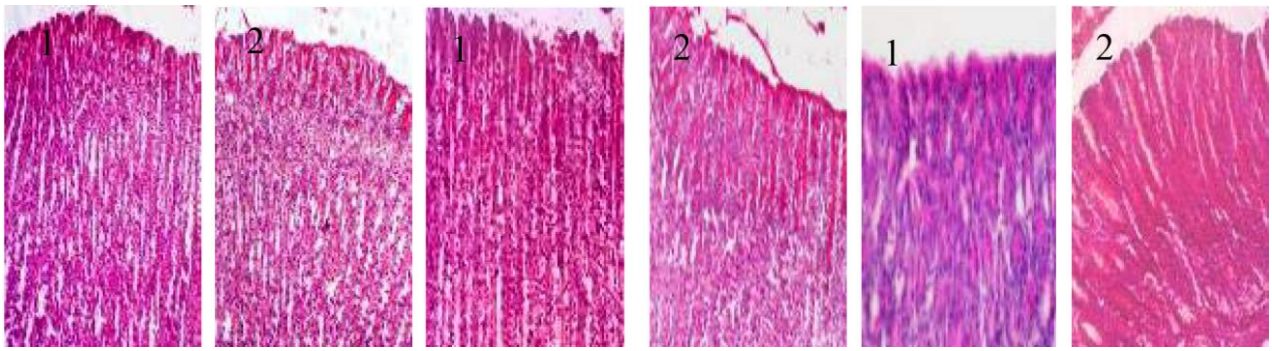
Fig. 1. The gastric mucosa of intact rats and after exposure to acetylsalicylic acid: *a*, *b* – fundus parts; *c*, *d* – prepyloric parts; *e*, *f* – pyloric parts; 1 – significant or sufficient content of PAS-positive material in the mucous-forming cells in the all parts of the stomach; 2 – the absence or a distinct decrease in PAS-positive material in the cells in the all parts of the stomach. PAS-reaction. ×200

The cytoplasm of the cellular elements of the prepyloric region is also rich in PAS-positive material (Fig. 1, *c*). In the pyloric region of the stomach, the layer of epithelium is higher, the gastric fossae are deeper and wider.

The pyloric glands are quite loose, connective tissue layers between them are more expressive. The glandular tubes are lined with one layer of cells, their cytoplasm was clearly PAS-positive, which indicates a significant mucoid secretion in them (Fig. 1, *e*).

In all rats with ASA-induced gastropathy in the investigated sections of the stomach, a violation of the mucus-forming function of the pathogenic epithelium was detected. When setting up a PAS-reaction, a sharp decrease in cytoplasmic staining intensity was found, the content of neutral mucopolysaccharides was uneven and significantly reduced. In cells that are flattened in shape, it is practically absent; in areas with relatively intact epithelium, the PAS-positive material occupied only the marginal zones of the cytoplasm (Fig. 1, *b, d, f*).

After the introduction of dry cabbage extract in the overwhelming majority of rats, secretion in the cells of the integumentary-patchy epithelium in most parts of the mucous membrane approached normal, in limited areas with flattening of the cells was slightly reduced (Fig. 2, *a, c, e*).



a *b* *c* *d* *e* *f*

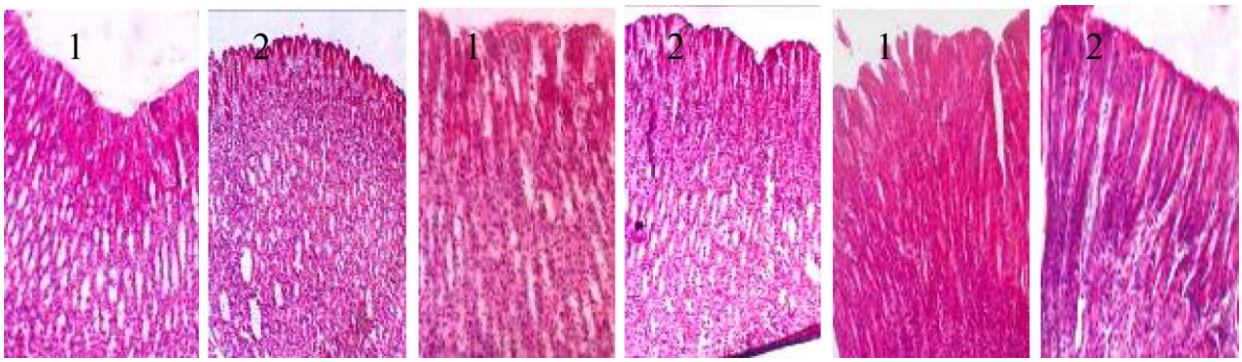
Fig. 2. The mucous membrane of the stomach of rats, which was given cabbage extract and omeprazole on the background of an ulcerative lesion: *a, b* – fundus parts; *c, d* – prepyloric parts; *e, f* – pyloric parts; 1 – restoration of the content of PAS-positive material in the covering-dummy epithelium of different parts of the stomach; 2 –normal intensity of the PAS-reaction in the integumentary-patchy epithelium in the all parts of the stomach. PAS-reaction. ×200

With the introduction of omeprazole against the background of an ulcer, an intense reaction is well detected in the epithelial cells of the superficial-fossa epithelium in all examined mucosal areas (Fig. 2, *b, d, f*). However, its severity is reduced in rats with a violation of the integrity of the integumentary epithelium.

In our experiments, the combined administration of cabbage extract and omeprazole against acetylsalicylic acid almost completely restored the state of the mucous membrane in all rats. The intensity of the Schick reaction of the superficial- patchwork epithelium of the mucous membrane did not differ from the intact control (Fig. 3, *a, c, e*).

With the introduction of altan in all rats, the PAS-reaction in the intact areas of the mucous membrane is increased relative to the control pathology (Fig. 3, b, d, f), but given that the areas with damage to the epithelial cover in rats are still quite voluminous, it can be said that the mucous barrier is not fully restored.

A semi-quantitative assessment of the condition of the mucous membrane of the glandular section of the stomach of rats confirmed that dry cabbage extract reliably restored the secretion of neutral mucopolysaccharides in the gastric mucosa of rats with NSAID gastropathy (Table 2).



a *b* *c* *d* *e* *f*

Fig. 3. The gastric mucosa of rats, which, against the background of acetylsalicylic acid, was given a combination of cabbage extract + omeprazole and altan: *a, b* – fundus parts; *c, d* – prepyloric parts; *e, f* – pyloric parts; 1 – no changes in the intensity of the PAS-reaction in the pathogenic epithelium in the all parts of the stomach; 2 – moderate increase in the intensity of the PAS-reaction in cells of the covering-dimple epithelium in the all parts of the stomach. PAS-reaction. ×200

Table 2

The effect of dry extract of cabbage garden on the functional activity of mucus-forming elements of the stomach in rats with acetylsalicylic acid, points, Me (LQ;UQ)

Groups of rats	IC	CP	CP + cabbage extract, 50 mg/kg	CP + omeprazole, 2,5 mg/kg	CP + cabbage extract + omeprazole	CP + altan, 1 mg/kg
Power PAS-reaction outside zones destruction	3 (3;3)	1 (1;1)*	3 (3;3)**	3 (2;3)**	3 (3;3)**	3 (2;3)**

*Note: * – differences are statistically significant with respect to group IC, p<0.05; ** – differences are statistically significant with respect to group CP, p <0.05*

According to the severity of positive effects on the slime cell function cover-pit epithelium of the stomach mucosa by garden cabbage dry extract, and its combination with omeprazole is not only not inferior to the proton pump inhibitor, but in a few his superior.

5. Discussion of the research results

Experimental gastric ulcer caused by acetylsalicylic acid is known to be a subchronic lesion of the mucous membrane in terms of duration and nature of the lesion and is considered as a model of an ulcer that has a clinical analogue in people who take aspirin. Acetylsalicylic acid destroys the protective layer of mucus, inhibits glycoprotein biosynthesis, promotes the back diffusion of hydrogen ions into the thickness of the mucous membrane, which is accompanied by local release of histamine and a violation of the integrity of the capillary wall [2]. At the initial stage of gastric damage, acetylsalicylic acid is characterized as "irritation" gastritis. These phenomena cause focal necrosis, as a consequence, a violation of the protective-barrier properties of the mucous membrane, epithelial desquamation occurs, and massive fields of hemorrhagic erosions and ulcers appear [13].

In our experiment, the antiulcer activity of dry cabbage extract was at the level of omeprazole, 83 %, and significantly exceeded the gastroprotective effect of the herbal drug altan (antiulcer activity – 72 %).

It should be noted that proton pump inhibitors, which are most often used for the prevention of gastropathy caused by nonsteroidal anti-inflammatory drugs, in a clinical setting do not reduce the risk of developing ulcerative lesions in all patients [19], which was also confirmed by our experimental data.

In recent years, to reduce complications due to NSAIDs propose to combine proton pump inhibitors with a synthetic analogue of prostaglandin E1, misoprostol, the use of which is limited to serious adverse reactions (diarrhea, arrhythmia, bronchospasm) and insufficiently studied mucoprotective rebamipide [20, 21].

This was the basis of the evaluation of the gastroprotective effect of the combination of the dry extract of cabbage garden and omeprazole which showed anti-ulcer activity of 94 %.

Among the factors of gastroprotection a significant role has sufficient functional activity of the mucous layer, which main component is mucus – mucoid secret that provides the protective function of the mucous barrier [22].

To characterize the functional activity of the slime of the elements of the stomach was assessed by the intensity of the PAS-reaction in fundus, prepyloric and pyloric parts of the stomach.

In animals of the control group, which were injected with acetylsalicylic acid, the violation of the protective mucous barrier of the stomach was established, corresponds to the typical microscopic picture of NSAID-gastropathy [23].

According to the results, the dry cabbage extract almost completely normalized mucoid secretion, the intensity of the PAS-reaction with omeprazole was slightly reduced.

Some studies have shown the effectiveness of proton pump inhibitors when used simultaneously with mucoprotectors, although the latter are not mandatory means of preventing and treating ulcerative injuries of the stomach [22].

The combination of the dry cabbage extract with omeprazole restored the state of the gastric superficial-foveolar epithelium to the maximum; the comparison drug altan showed the minimal intensity of the PAS-reaction.

The analysis of the obtained data allows us to conclude that one of the mechanisms that accounts for the pronounced gastroprotective effect of dry cabbage extract for subchronic gastric lesions is its ability to enhance mucus formation by cells of the integumentary-patchy epithelium of the stomach.

Thus, the results of the study showed that combined therapy with dry extract of cabbage and alprazolam significantly increased the antiulcer effect compared with the monotherapy with each drug. Dry extract of cabbage can be attributed to gastroprotection acetylsalicylic acid ulcerogenesis, which allows to prove the possibility of preventive treatment in the treatment of NSAIDs, and also in the treatment of peptic ulcers caused by aspirin.

To obtain more accurate conclusions on the antiulcer properties of the dry cabbage extract, it is appropriate and necessary to investigate its activity on an experimental model of chronic gastric ulcer and to find other mechanisms of action.

6. Conclusions

On the model of gastric lesions of rats with acetylsalicylic acid dry extract of cabbage showed antiulcer effect and not inferior to the proton pump inhibitor omeprazole and the exceeded action of altan. The combined use of dry extract of cabbage and omeprazole showed a high preventive effect on negative action of NSAIDs on the gastric mucosa.

One of the mechanisms gastroprotective action of dry extract of garden cabbage is its ability to strengthen mucoid secretion of the cells cover-pit epithelium of the stomach.The obtained results indicate the expediency of

further studies of dry extract of garden cabbage in the complex therapy of peptic ulcer disease.

Conflict of interest

Author has no conflict of interest to declare.

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