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## Experimental study of antiulcerogenic action of *Chamaenerion angustifolium* the aspirin induced gastric ulcer modeling the rats

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### Abstract

For the treatment of gastric ulcer and duodenal ulcer, a number of drugs is used with a wide range of effects - anti-inflammatory, reparative, analgesic, hemostatic activities. Considering that most of them are synthetic with a significant number of side effects and a number of contraindications, the alternative is to search for new drugs, including plant origin. A well-known medicinal plant rosebay willow herb (*Chamaenerion angustifolium* L.), which contains a significant amount of phenolic compounds (tannins, flavonoids, hydroxycinnamic acids) is an object of interest. According to the literature, it is used in traditional medicine for treatment of gastric ulcer.

It was experimentally established that lyophilized extract of rosebay willow at dose 20 mg/kg proved a significant gastroprotective effect in model of simulated erosive and haemorrhagic gastric mucosa damage caused by acetylsalicylic acid. In cases of administration of lyophilized extract of rosebay willow, the severity of inflammation of gastric mucosa of the rats reduced as well as the intensity of the lipid peroxidation processes up to the physiological level, the reduced glutathione pool and the energy balance of gastric cells restored. Moreover, for this model the investigated extract proved to have a normalization effect on the parameters of coagulation link of haemostasis that confirmed the expediency of the use of lyophilized extract of rosebay willow in concomitant therapy for prevention of haemorrhage in cases of gastro duodenal ulcers.

**Keywords:** Gastric ulcer, lyophilized extracts of rosebay willow, aspirin gastric ulcer model, lipid peroxidation

### 1. Introduction

Digestive disorders cause considerable economic and social impact on our society. Gastroduodenal ulcer (GU) dominates among these pathologies, which have been a topical issue of healthcare for more than 150 years. The share of GU is 1.7-16% among the digestive disorders. The incidence of GU in Western Europe is an average of 8.2% [1].

Thus, despite great success in gastroenterology in recent decades, gastro duodenal ulcer (GU) has been a common disease followed by significant lethality and lots of complications [1,2]. For the treatment of GU a wide range of drugs is used [3]; most of them are synthetic and may cause a serious number of side effects and have some contraindications [4,5].

We believe that herbal medicinal products (HMP) may facilitate solving this problem. In gastroenterology, the HMP can be used in the period of exacerbation of the disease as a means of complementary therapy in combination with basic drugs as well as therapeutic and prophylactic agents at the early stages of the disease, during the course of anti-relapsing therapy and in the period of rehabilitation. Considering that the HMP include different chemical composition and have a broad pharmacotherapeutic range, they can implement the requirements of rational pharmacotherapy for ulcer development [6].

A well-known medicinal plant rosebay willow herb (*Chamaenerion angustifolium* L.), which contains a significant amount of phenolic compounds (tannins, flavonoids, Hydroxycinnamic acids) [7] is an object of interest. According to the literature, it is used in traditional medicine for treatment of GU [8].

Therefore, the aim of this study was this experimental study was to investigate the antiulcerogenic action (AUA) of the lyophilized extract of rosebay willow herb (LERW) on the aspirin gastric ulcer model; it can be considered as a model of the disease with a clinical analogue in the patients, who take acetylsalicylic acid (aspirin) durably [4,9]

Previous studies have proved that rosebay willow herb has a significant gastro protective effect in cases of acute stomach damage caused by ethanol-prednisolone [10].

## 2. Material and Methods

The studies were carried out following the rules of the “European Convention for the Protection of Vertebrate Animals, Used for Experimental and Scientific Purposes” (Strasbourg, 1986) [11, 12]. During the experiment, the animals were kept in vivarium at t° 18-240 °C, humidity 50-60%, natural day-night cycle, in plastic cages, on a balanced diet in accordance with current standards.

The most effective dose for the gastro protective activity of the lyophilized extract of rosebay willow herb (LERW) was determined on the model of subchronic erosive-haemorrhagic damage of gastric mucosa caused by acetylsalicylic acid (ASA) [13, 14, 15]. All experimental animals were divided into 6 experimental groups comprising 5 animals in each group: the 1<sup>st</sup> group –the intact control: the unaffected animals; the 2<sup>nd</sup> group –the control pathology: animals with simulated ulcerative damage by ASA; groups 3-5–the animals, which with underlying simulated pathology were administered with the lyophilized extract of rosebay willow herb (LERW) at doses of 5, 10 and 20 mg/kg, respectively; the 6<sup>th</sup> group –the animals, which with underlying simulated pathology were administered with a comparator–infusion of Gastro fit tea at a dose of 3.8 ml/kg.

The sub chronic erosive-haemorrhagic damage of gastric mucosa was simulated by intragastric administration of ASA at a dose of 150 mg/100 g of body weight once a day for three days to the male white rats, 160-220 g in weigh. Before administration of the ASA, the animals were kept without food for 12 hours, with free access to water.

The LERW was administered intragastrically by special tube in a treatment-prophylactic mode (1 hour before and 1 hour after administration of the ASA). The dose of the comparator was considered in relation to the daily dose for humans, taking into account the body area and body weight of the animals according to the method [16].

On the fourth day, all animals were undergoing inhalation anesthesia and sacrificed by decapitation. Blood plasma for biochemical examination was taken for biochemical analysis, the stomach was removed as well; it was cut along a lesser gastric curvature, the gastric mucosa (GM) was investigated using a magnifying glass.

Macroscopic evaluation of the severity of GM damage was carried out according to the score system: 0 points –no visible damage; 1 point –presence of swelling or haemorrhages, 1-3 small ulcers; 2 points – several (more than 3) small ulcers or 1 ulcer of significant size; 3 points – ulcers of significant (up to 4 mm in diameter) sizes; 4 – several large ulcers; 5 points – perforated ulcer.

In each group, the average degree of damage (DD) of gastric mucosa was evaluated that was calculated as the arithmetic mean of the sum of the scores in the group. Anti-ulcer activity was assessed by the formula:

$$AA = \frac{DM_{control} - DM_{study}}{DM_{control}} \times 100$$

Where AA – anti-ulcer activity;

DM<sub>study</sub> – the average degree of gastric mucosa damage in the animals of experimental group;

DM<sub>control</sub> – the average degree of gastric mucosa damage in the animals of control group.

In blood plasma, the parameters of blood coagulation system of rats were evaluated: fibrinogen content, prothrombin time, and activated partial thromboplastic time (aPTT) by coagulometric analyser RT-2204C (Italy) using kits produced by RENAMNPO Company (Russia).

The content of TBA-reactive substances (TBARC) and reduced glutathione (RG) [17, 18] was determined in GM of the rats. The content of succinate dehydrogenase [19] in GM was determined in order to evaluate the state of energy supply of gastric cells.

## 3. Results and Discussion

The results of determination of the antiulcer genic action of LERW are presented in Table 1. The studies proved that in the control group the fasting administration of the ASA solution caused damage of gastric mucosa in 100% of the animals. A massive oedema, significant hyperaemia, deep and large haemorrhagic erosions and ulcers of irregular shape were evidenced. The severity of GM damage varied from 2 to 3 points (Table 1).

**Table 1:** Influence of LERW on the gastric mucosa in cases of subchronic erosive-haemorrhagic damage caused by acetylsalicylic acid. Macroscopic evaluation, n=5

Groups of animals	Descriptive statistics	Parameters		
		Degree of GM damage	% of animals with ulcers	AUA, %
Intact control	M (min; max)	0 (0; 0)	0 (0/5)	–
	Me (Q25; Q75)	0 (0; 0)		
Control pathology	M (min; max)	2,6 (2; 3)	100 (5/5) *	–
	Me (Q25; Q75)	3 (2; 3)		
LERW, 5 mg/kg	M (min; max)	2,4 (2; 3) *	100 (5/5) */#	8
	Me (Q25; Q75)	2 (2; 3)		
LERW, 10 mg/kg	M (min; max)	2,4 (2; 3) *	100 (5/5) */#	8
	Me (Q25; Q75)	2 (2; 3)		
LERW, 20 mg/kg	M (min; max)	0,8 (0; 1) *	80 (4/5) */**	69
	Me (Q25; Q75)	1 (1; 1)		
Tincture of Gastro fit tea, 3.8 ml/kg	M (min; max)	1 (1; 1) **	100 (5/5) */**	61
	Me (Q25; Q75)	1 (1; 1)		

Notes:

1. \*, statistically significant differences relating to the parameters of intact control,  $p < 0.05$ ;

2. \*\*, statistically significant differences relating to the parameters of control pathology,  $p < 0.05$ ;

N, number of animals in a group.

LERW at the doses of 5 and 10 mg/kg proved a poor gastro-protective effect: the severity of the damage decreased to 2.4

points. The ulcerations were present in all animals, the same as in the control group, but the number of animals with the

maximal 3 points damage severity was in 2 of 5 animals of the study groups versus 3 of 5 animals of the control group. Antiulcerogenic activity of LERW at doses 5 and 10 mg/kg was only 8%.

The increase in the dose of LERW up to 20 mg/kg caused the improved anti-ulcer properties of the extract. The administration of the extract in the treatment-prophylactic mode stimulated reparative processes in the areas of ulcer defect. With the LERW, the degree of GM damage in all animals with visible changes in mucosa was 1 point (only oedema was evidenced, no folding and/or 1-2 small ulcerations). The severity of GM damage decreased in on average 3.2 times and was 0.8 points. In one animal of 5 the mucosa was in norm, without visible damage. The antiulcerogenic activity of LERW at a dose of 20 mg/kg was 69% on this model. The comparator Gastrofit tea proved antiulcerogenic activity of 61%.

Thus, the results of the experiment proved that for the simulated subchronic erosive-hemorrhagic GM damage caused by ASA, the most significant gastroprotective effect of LERW was revealed at a dose of 20 mg/kg. The efficacy of LERW was not worse than that of the comparator Gastrofit tea.

In recent times it has been established that the oxidative stress and the antioxidant system imbalance are crucial in the pathogenesis of GU [20, 21]. Intensification of formation of free radicals, reactive oxygen intermediates, and prooxidants leads to increased permeability and damage to cell membranes, inhibition of cell fission and regeneration, intracellular metabolic disorders and energy imbalance [22]. Many clinical and experimental studies have established a close correlation between the level of oxidative stress and the severity of gastro

duodenal ulcer [23, 24].

Taking into account these results, the content of the secondary products of lipid peroxidation: TBA-reactive substances (TBARC), was determined in the GM of the rats, as well as the content of reduced glutathione for evaluation of the state of antioxidant protection of the animals. It was established that in cases of experimental erosive-hemorrhagic GM damage caused by ASA, in the homogenate of GM of the rats of control group the content of TBA-reactive substances statistically significantly increased in 2.2 times, the content of RG tended to decrease (Table 2). Accumulation of the content of secondary products of lipid peroxidation in GM with the simultaneous decrease of RG, one of the most important components of the antioxidant system, proved the activation of the processes of peroxidation and reduction of antioxidant protection. The results coincide with other researches on the development of prooxidant-antioxidant imbalance in cases of gastric ulcer [23, 24, 25].

The changes of the energy status of cells, which is directly related to the functioning of mitochondria, are crucial in the pathogenesis of gastric ulcer. These organelles react sensitively to negative effects by changes in activity of membrane-bound enzymes. Succinate dehydrogenase (SDG) is an enzyme of the internal membrane of mitochondria that catalyses the reversible oxidation of amber acid to fumaric acid in the tricarboxylic acid cycle that results in the formation of ATP molecules. In cases of erosive and haemorrhagic damage of GM with acetylsalicylic acid the energy imbalance of cells takes place that is proved by the enzymatic activity of SDG compare to the intact animals (Table 2).

**Table 2:** The state of the lipid peroxidation/antioxidant system and energy supply in gastric mucosa homogenates of rats in cases of subchronic erosive and haemorrhagic damage of gastric mucosa caused by acetylsalicylic acid, n=5 (M±m)

Groups of animals	Parameters		
	TBA-reactive substances, $\mu\text{mol/g}$	RG, $\mu\text{mol/g}$	SDG $\mu\text{mol/g}$
Intact control	26.67±3.47	3.52±0.29	1.45±0.09
Control pathology	57.43±5.41*	2.77±0.17	0.71±0.14*
LERW, 5 mg/kg	32.82±2.49**	3.06±0.30	1.07±0.11*/**
LERW, 10 mg/kg	29.74±4.43**	3.99±0.47	1.05±0.06*/**
LERW, 20 mg/kg	26.15±5.1**	3.90±0.21**	1.51±0.09**
Tincture of Gastrofit tea, 3.8 ml/kg	36.41±5.94**	3.13±0.29	1.13±0.11*/**

**Notes:**

1. \*, statistically significant differences relating to the parameters of intact control,  $p < 0.05$ ;
  2. \*\*, statistically significant differences relating to the parameters of control pathology,  $p < 0.05$ ;
- n – Number of animals in a group.

The prophylactic and therapeutic administration of LERW into the rats with experimental GM damage at the dose range of 5-20 mg/kg contributed to a statistically significant decrease in TBA-reactive substances content in GM homogenates compare to the control pathology. Along with that, the increased content of RG was evidenced. It should be noted that the most significant decrease in the TBA-reactive substances content and the reduced glutathione pool took place in case of LERW administration at a dose of 20 mg/kg. The improvement in energy supply of GM cells was proved by normalization of succinate dehydrogenase enzymic activity in case of LERW administration at a dose of 20 mg/kg, since the succinate dehydrogenase was an important catalyst of energy metabolism in the body.

In cases of administration of the tincture of Gastrofit tea, the dynamics of the studied parameters was similar to that in the groups of animals administered with LERW at doses of 5 and

10 mg/kg (Table 2).

In the pathogenesis of GU, the blood clotting disorder is crucial. It is established that during the exacerbation of GU the development of hypo coagulation and increase in total fibrinolytic activity takes place, as well as prolongation of blood coagulation, decrease in prothrombin index, decrease in plasma tolerance to heparin and a slight increase of fibrinolytic activity [26]. Determination of some parameters of the coagulation link of hemostasis proved that, in cases of erosive and hemorrhagic DM damage by acetylsalicylic acid, a significant disorder of blood coagulation system takes place, as evidenced by a statistically significant prolonged prothrombin and activated partial thromboplastin time (aPTT, the duration of formation of blood clot after joining of calcium chloride and other reagents to plasma) (Table 3). It should be noted that, among other clinical indicators, aPTT is the most sensitive parameter of blood coagulation, which

reveals the so-called internal pathway and general cascade of blood coagulation of humans and animals.

The development of any acute inflammation is followed by the release of proteins of acute phase. Acute response to inflammation is present in order to re-establish the disturbed homeostasis by controlling haemorrhage, limiting a damage area and resorption of necrotic tissues, binding and removing excessive amount of tissue proteases and exogenous substances, creating conditions for reparation. Acute response is a complex of local and systemic reactions, which are mediated by various mediators: cytokines, prostaglandins, kinins, hormones. The significance and nature of a response depend on the activity of a process (inflammation, trauma and other pathological effect) [27].

The inflammatory proteins (IP) are significant for nonspecific defence of the body. The main task of the IP is to organize the reparation processes in the damage area [28].

Fibrinogen is one of the inflammatory proteins, which is

synthesized in the liver like other proteins are (C-reactive protein (CRP), Orosomucoid, Ceruloplasmin, ferritin, haptoglobin, etc.). In our experiment, in cases of subchronic erosive-haemorrhagic GM damage, the increase in the level of fibrinogen twice was evidenced compare to the intact animals (Table 3) that can be regarded as an increased response of the body to acute inflammation in cases of gastric damage by ASA. Analysing the data attained, it should be noted that there is some difference between the fibrinogen content and the aPTT (Table 3). It is established that the aPTT index depends on the number of blood plasma factors II, V, VII, X, XI, XII, as well as the concentration of fibrinogen. However, taking into account the significance of fibrinogen as an inflammation protein, it can be assumed that the increase of its concentration in plasma of the animals with erosive and haemorrhagic GM damages is a compensatory and adaptive response of the body, which is aimed at accelerating the reparation of GM of the rats.

**Table 3:** Influence of the lyophilized extract of rosebay willow herb on the parameters of blood coagulation system of rats in cases of subchronic erosive and haemorrhagic damages of gastric mucosa caused by acetylsalicylic acid, n=5 (M±m)

Groups of animals	Parameters		
	Fibrinogen, g/l	Prothrombin time, sec	aPTT, sec
Intact control	0.92±0.03*	15.74±0.36	22.38±1.26
Control pathology	1.96±0.08*	29.75±3.11*	40.88±2.44*
LERW, 5 mg/kg	1.66±0.12*	18.62±0.81**/#	32.70±1.54**/**
LERW, 10 mg/kg	1.36±0.15**/**	25.36±2.75*	34.88±1.66**/**
LERW, 20 mg/kg	1.39±0.23**/**/#	20.00±0.84**/#	29.84±1.61**/**/#
Tincture of Gastrofit tea, 3.8 ml/kg	1.87±0.14*	29.10±1.53*	37.90±2.01*

**Notes:**

1. \*, statistically significant differences relating to the parameters of intact control,  $p < 0.05$ ;
  2. \*\*, statistically significant differences relating to the parameters of control pathology,  $p < 0.05$ ;
  3. #, statistically significant differences relating to the parameters of the comparative drug of tincture of Gastrofit tea,  $p < 0.05$ ;
- N, number of animals in a group.

In cases of administration of the investigated extract at the doses ranging from 5 to 20 mg/kg, the normalization of the studied parameters was evidenced (Table 3). The highest efficacy of LERW regarding normalization of the parameters of haemostasis of the rats was established at a dose of 20 mg/kg. In cases of administration of the extract at a dose of 20 mg / kg, the prothrombin time and aPTT were statistically significantly lower compare to the control pathology and the comparative agent of Gastrofit tea tincture (Table 3). Simultaneously with normalization of the parameters of coagulation link of haemostasis, a decrease in fibrinogen concentration took place that proved the reduction of inflammation severity of GM of the rats. This was confirmed by a macroscopic analysis of the GM (the severity of inflammation was reduced to one point, see Table 1).

#### 4. Conclusions

It was established that lyophilized extract of rosebay willow at dose 20 mg/kg proved a significant gastro protective effect in model of simulated erosive and haemorrhagic gastric mucosa damage caused by acetylsalicylic acid. In cases of administration of lyophilized extract of rosebay willow, the severity of inflammation of gastric mucosa of the rats reduced as well as the intensity of the lipid peroxidation processes up to the physiological level, the reduced glutathione pool and the energy balance of gastric cells restored. Moreover, for this model the investigated extract proved to have a normalization effect on the parameters of coagulation link of haemostasis that confirmed the expediency of the use of lyophilized

extract of rosebay willow in concomitant therapy for prevention of haemorrhage in cases of gastro duodenal ulcers.

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