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DEVELOPMENT AND OPTIMIZATION OF THE MANUFACTURING TECHNOLOGY FOR "ANTIOXIM" CAPSULES

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ABSTRACT

This scientific article investigates the biopharmaceutical properties of a newly recommended three-component capsule formulation, "Antioxim," using both in vitro and in vivo methodologies. The experimental studies evaluated the dry extract of "Antioxim" obtained using 40% and 70% ethyl alcohol. The in vitro results demonstrated that the three-component dry extract effectively prevents the autooxidation of adrenaline, confirming its strong antioxidant activity. Additionally, in vivo evaluations of acute toxicity showed that the "Antioxim" dry extract exhibits no toxic clinical signs and can be classified as a non-toxic substance. Overall, these findings highlight the therapeutic potential and safety profile of "Antioxim" capsules for further biomedical applications.

Introduction: The Republic of Uzbekistan has a large and rich resources of medicinal plant raw materials. The development of the pharmaceutical industry of the republic is the creation of phytopreparations based on local medicinal plant raw materials, the development of highly efficient technologies for their production and introduction into industrial production. One of the main directions of the development of pharmaceutical science and practice is the improvement of the technology of extraction of medicinal plant raw materials (LRS) in order to increase the yield of BAS, the quality and expansion of the range of phytopreparations [4,7,8,9].

When conducting research on the intensification of technological processes, the development of phytopreparation technology, it is relevant to maximize the potential of both known and used medicinal plants and new promising species. The main criterion of the quality indicator and the value of any drug ultimately in the manifestation of the therapeutic effect [3,5,6].

One of the main biopharmaceutical criteria determining the therapeutic efficacy of a medicinal substance is its bioavailability. Bioavailability is an objective characteristic of therapeutic efficacy. The initial stage of the bioavailability study is to determine the release time of the drug from the dosage form. It has been established that the solubility test characterizes the bioavailability of the drug in the first approximation (since it is an instrumental method for determining the bioavailability of the drug), since in practice there is a very frequent correlation between the rate of dissolution and absorption [5,810,17,22].

Among such drugs, such medicinal plants as Melissa officinalis, Saffron (Crocus sativus) and Hypericum perforatum are widely used in medical practice. Complex phytopreparations obtained on the basis of the above plants under the code name "Antioxim", used in medical practice as an antihypoxant, should also be referred to this class of substances.

"Antioxim" is a collection, a complex phytopreparation containing 3 plants in its composition: Melissa officinalis, Saffron and Hypericum perforatum. The three-component dry extract "Antioxim", developed at the Department of Industrial Technology of Medicines at Tashkent Pharmaceutical institut, was obtained on 40% ethyl alcohol based on a three-component plant composition. Saffron (Crocus sativus) has a restorative effect on the body. It rejuvenates cells, normalizes the work of the genitourinary and nervous systems, cleanses the kidneys and improves blood composition, normalizes the menstrual cycle, treats diseases of the reproductive system. Saffron stigmas are also used to strengthen labor efforts and cleanse the female body after childbirth. This amazing spice restores brain cells, improves intellectual abilities. The use of saffron stigmas is recommended for atherosclerosis, ischemic disease, angina pectoris and hypertension. Saffron has an excellent diuretic effect, thanks to which it is used in the treatment of cystitis, urethritis and urolithiasis.

Saffron is used to treat children's respiratory diseases, as it has an antiseptic and expectorant effect. Externally, the plant is used to treat eye diseases, inflammation of the mammary glands, testicles and hemorrhoids, nail fungus. In addition, saffron improves appetite and improves the digestive process.

Melissa officinalis is a sedative with anxiolytic, antidepressant, antispasmodic, immunomodulatory, antiviral properties. A wide range of therapeutic effects of Melissa officinalis preparations is due to the content of various biologically active substances: a pronounced sedative effect is described for citronellal, and antispasmodic properties are described for geraniol and citronellol. It should be considered as dietary supplements responsible for antiviral, immunomodulatory, antihistamine, antioxidant and antimicrobial properties of the substances of this plant.

Hypericum perforatum - contains amentoflavone, a non-selective blocker (antagonist) of opioid kappa receptors, as well as the benzodiazepine segment of GABA receptors, which to some extent

explains the antidepressant and anti-intoxicating effects on the psyche used in the treatment of depression. Hyperforin is an inhibitor of the reuptake of monoamines, including serotonin and dopamine, which also facilitates depression. Hypericin selectively inhibits the enzyme dopamine-beta-hydroxylase, which increases the level of dopamine. In previous studies, we obtained a dry extract from the above-injected plant "Antioxim" and determined its qualitative properties.

The experimental study of the bioavailability of the recommended drugs was carried out starting with in vitro experiments and ending with in vivo experiments.

The purpose of these studies was to study the biopharmaceutical properties of the "Antioxim" capsules obtained by us with the recommended composition and technology.

Materials and methods: The object of the study is a three-component dry extract "Antioxim" (obtained on 40% and 70% ethyl alcohol). The antioxidant activity (AOA) of the dry extract under study was determined photometrically and evaluated by inhibiting the reaction of autoxidation of adrenaline in vitro, as well as its inhibition of the formation of active oxygen form (ROS) for a fixed time.

The optical density (OP) of the studied extract was measured using a UV-1800 Shimadzu spectrophotometer, Japan in a cuvette with a layer thickness of 10 mm at a wavelength of 347 nm for a time from 30 seconds to 10 minutes with rapid stirring. The acute toxicity of "Antioxim" was studied in vivo on 12 white mice, weighing 19-21 g, of mixed sex. The presented sample of the BUD was administered in the form of a tincture (the tincture was prepared in a ratio of 1/10). The animals were divided into groups of 6 heads and tincture was administered once intragastrically in doses of 15 ml/kg and 25 ml/kg.

To determine the specific activity by the in vivo method, 36 heads of white male rats with a body weight of 180-200 g were selected. For the experiment, the animals were divided into 6 groups. The model of paracetamol hepatitis was caused by a single intragastric administration of paracetamol to control and experimental groups at a dose of 1000 mg/kg.

The experimental part

Study of acute toxicity of "Antioxim" capsulesby in vitro method.

2.0 ml of 0.2 M carbonate buffer buffer (Na2CO3-NaHCO3) with pH = 10.65 containing 56 mg/ml of 0.18% epinephrine (epinephrine) hydrochloride solution was introduced into the cuvette, and 0.06 ml of 10% solution of the studied extract was added. The same solution, but not containing an antioxidant, was used as a control sample.

Antioxidant activity (AOA) was expressed as a percentage, depending on the rate of inhibition of epinephrine autooxidation and calculated using the following formula:

$$AOA = \frac{(D1-D2)}{D1} \times 100\%$$

where:

D1 is the optical density of the epinephrine hydrochloride solution added to the buffer;

D2 is the optical density of the solution after the addition of the test extract.

Statistical data were evaluated using the t-Student criterion.

The results obtained: when adding a 10% solution of the three-component dry extract "Antioxime" to a buffered solution with adrenaline, the optical density of 10% of the test sample after 3 minutes was less than that of the control sample and the antioxidant activity of the extract was 35.2% and 60.7%, respectively, and after 10 minutes the AOA was 59.5% and 79.5%, respectively, compared with the control sample. It is known that if the AOA value is more than 10%, then this indicates the presence of antioxidant activity [5].

when adding a 10% solution of the three-component dry extract "Antioxime" to a buffered solution with adrenaline, the optical density of the test sample after 3 minutes was less than that of the control sample and the antioxidant activity of the test extract was 60.7%, and after 10 minutes the AOA was 79.5% compared to the control sample.

It is known that if the AOA value is more than 10%, then this indicates the presence of antioxidant activity. Since the AOA of the studied extract was more than 10%, especially in high concentrations, the extract has an antioxidant property. Since the AOA of the studied extract was more than 10%, especially in high concentrations, the extract has an antioxidant property.Table 1 shows the data obtained**.**

Table 1

Results determination of antioxidant activity of dry extract "Antioxim"

Samples	Optical density		AOA, %	
	3 mines	10 mines	3 mines	10 mines
Control sample	0,165±0,004	0,410±0,005	-	-
10% dry extract "Antioxime" (obtained on 40% ethyl alcohol)	0,107±0,002	0,167±0,024	35,2±1,2	59,5±5,6
10% dry extract "Antioxime" (obtained on 70% ethyl alcohol)	0,064±0,011	0,084±0,005	60,7±6,1	79,5±1,1

Study of acute toxicity of "Antioxim" capsules by in vivo method.

The animals were under continuous observation during the first hour, then under hourly observation during the first day of the experiment and once a day for the next 13 days of the experiment. As indicators of the functional state of animals, the general condition of mice and their behavior, the intensity and

nature of motor activity, the presence of seizures, coordination of movements, reaction to external stimuli and skeletal muscle tone, frequency and depth of respiratory movements, color of mucous membranes and pupil size, appetite, body weight, quantity and consistency of fecal masses were taken into account. During the experiment, the clinical condition of the animals was monitored: the presence/ absence of signs of poisoning, the time of their appearance, the death of mice. All experimental animals were kept in standard conditions, on a general diet with free access to water and food. After the experiment was completed, the average-lethal doses were determined (DL50) [5].

The results obtained: experiments showed that after a single intragastric administration of tincture in doses of 15 ml/kg and 25 ml/kg, no visible changes were observed in the behavior and functional state of animals. All mice are active, react to external stimuli, feed and water consumption was normal. There are no pathological changes in the condition of the coat and skin and there were no signs of intoxication. The consistency and amount of fecal matter are unchanged. There were no deaths among animals in this group until the end of the experiment.

The DL50 of the drugs was more than 25 ml/kg. The results of the experiment are shown in Table 2 3.

Table 2

Results determination of acute toxicity of dry extract "Antioxim"

Dry extract obtained with 40% ethyl alcohol

№ animals	Dry extract obtained with 40% ethyl alcohol				
	weight, g	Dose		the way of introduction	fatal outcome
		mg/kg	Мл		
1	19	6000	0,29	v/j	No
2	20		0,30		No
3	21		0,31		No
4	20		0,30		No
5	20		0,30		
6	21		0,31		
1	19	10000	0,48	v/j	No
2	19		0,48		No
3	21		0,51		No
4	20		0,50		No
5	20		0,50		No
6	19		0,48		No
LD_{50}		>10000 mg/kg			

Table 3

Results determination of acute toxicity of dry extract "Antioxim"

Dry extract obtained with 70% ethyl alcohol

№	Dry extract 70%

alive	weight, g	doza		the way of introduction	fatal outcome
		mg/kg	ml		
1	20	6000	0,30	v/j	No
2	19		0,29		No
3	20		0,30		No
4	21		0,31		No
5	20		0,30		No
6	21		0,31		
1	19	10000	0,48	v/j	No
2	21		0,51		No
3	19		0,48		No
4	20		0,50		No
5	19		0,48		No
6	20		0,50		No
LD_{50}		>10000 mg/kg			

Study of the specific activity of dry extract "Antioxime" by in vivo method.

Experimental groups of rats were injected with the studied extracts and an aqueous tincture of tea inside the stomach for 3 days.

Dry extract and tea were administered as follows:

Group 1 - intact - purified water per os;

Group 2 - control - paracetamol at a dose of 1000 mg/kg per os;

Group 3 - experimental - paracetamol at a dose of 1000 mg/kg + an aqueous solution of "Antioxim" (obtained on 40% ethyl alcohol) at a dose of 250 mg/kg per os;

Group 4 - experimental - paracetamol at a dose of 1000 mg/kg + an aqueous solution of "Antioxim" (obtained on 70% ethyl alcohol) at a dose of 250 mg/kg per os;

Group 5 - experimental - paracetamol at a dose of 1000 mg/kg + water tincture (1:10) of Antioxime tea at a dose of 10 ml/kg per os;

Group 6 - experimental - paracetamol at a dose of 1000 mg/kg + "Karsil" produced by Sopharma JSC, Bulgaria at a dose of 100 mg/kg per os.

The day after the last administration of dry extracts and tea, the rats were put to sleep under ether anesthesia for blood sampling. To assess the effect of extracts and tea on the processes of lipid peroxidation, the concentration of malondialdehyde (MDA) was determined by the method of M. Uchiyama and M. Mihara [3] on the SF UV-1800 spectrophotometer, Shimadzu Corp., Japan.

The obtained data were statistically processed using the STATISTICA program for Windows 95.

The results, of the experiment show that in the intact group the concentration of MDA was 2.42=0.23 nmol/ml. In the

control group, animals with paracetamol-induced hepatitis showed a significant increase in the content of MDA by 92.2% compared to the intact group. After the introduction of the dry extract "Antioxim" (obtained with 40% ethyl alcohol), the content of MDA in the blood decreased by 15.9% compared to the control group**.**

Under similar conditions, dry extract "Antioxim" (obtained on 70% ethyl alcohol) significantly reduced the content of MDA in the blood serum of rats by 19.6% compared to the control group.

After the introduction of Antioxim tea, the content of MDA in the blood decreased by 10.9% compared to the control group.

With the introduction of the drug "Karsil" produced by Sopharma, Bulgaria, the content of MDA in the blood significantly decreased by 27.9% compared to the control group.

The results showed that in the group of dry extract "Antioxim", obtained on 70% ethyl alcohol, the level of MDA was lower than in the group of dry extract "Antioxim", obtained on 40% ethyl alcohol and tea "Antioxim". This shows that the dry extract "Antioxim", obtained on 70% ethyl alcohol, more strongly suppresses free radical processes in the body.The results of the experiment are shown in Table 4.

Table 4

Groups	MDA, nmol/ml
Intact	2,42±0,23*
Control	4,65±0,34
"Antioxim" (obtained on 40% ethyl alcohol)	3,84±0,35
"Antioxim" (obtained on 70% ethyl alcohol)	3,98±0,11*
Antioxim Tea	3,24±0,25
"Karsil" produced by Sopharma JSC, Bulgaria	3,35±0,26*

Note:*- the difference in the confidence indicator when P<0,05 in comparison with the control group.

Conclusions:

1. Thus, an experimental study of the three-component "Antioxim" capsules (obtained on 40% and 70% ethyl alcohol) showed that the extract in vitro prevents auto-oxidation of epinephrine and has antioxidant activity.

2. An in vivo study of the acute toxicity of "Antioxim" capsules showed that the extract belongs to non-toxic substances.

3. Thus, an experimental study of the three-component "Antioxim" capsules (obtained on 40%, 70% ethyl alcohol) showed that the extracts have antioxidant activity. In the experiment, the antioxidant activity of the dry extract "Antioxim" obtained on 70% ethyl alcohol was more active than that of the dry extract "Antioxim" obtained on 40% ethyl alcohol.

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