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Investigation of Acute Toxicity of Tilorone Ointment for Topical Treatment of Herpes Virus Infection

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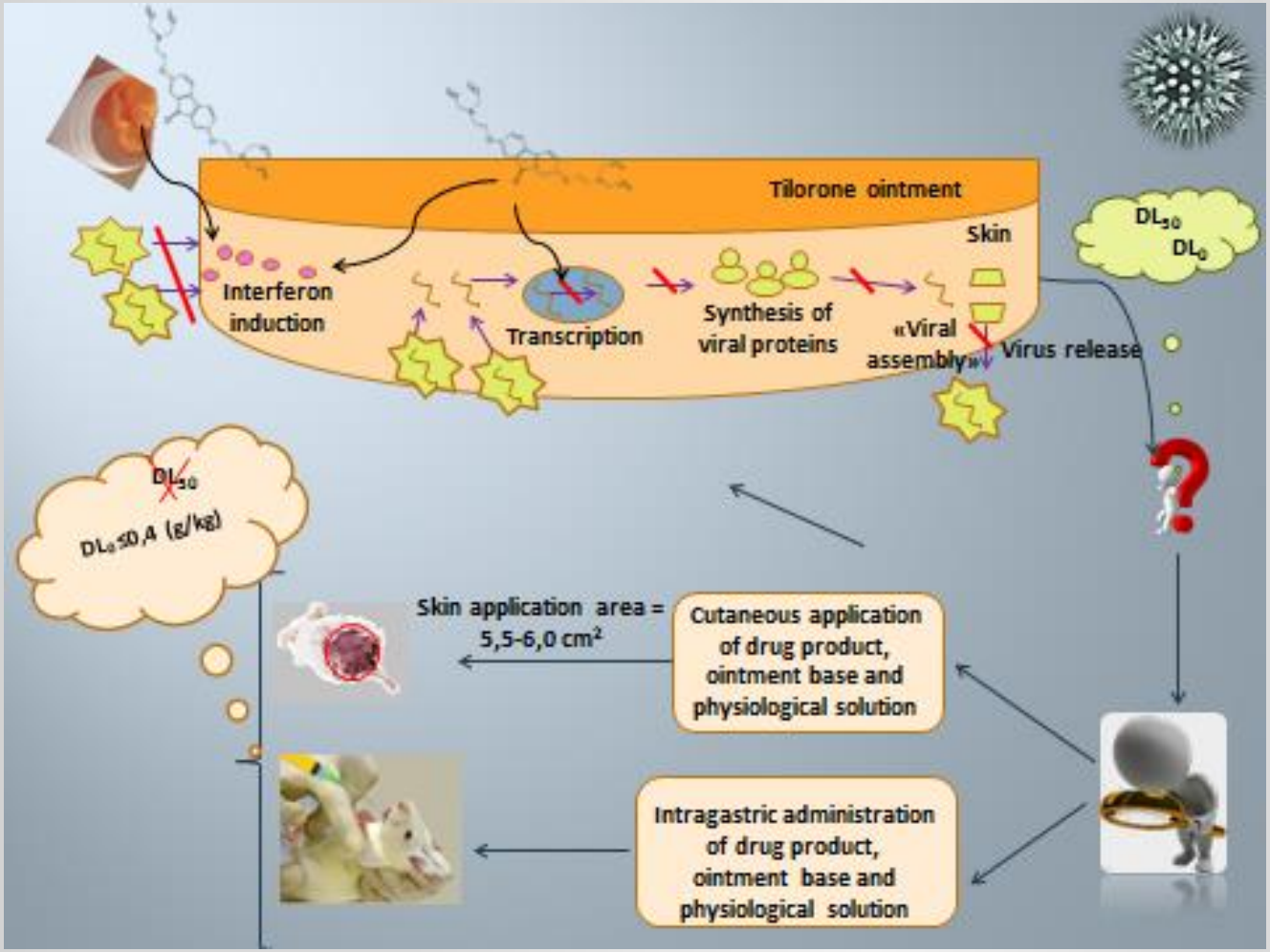
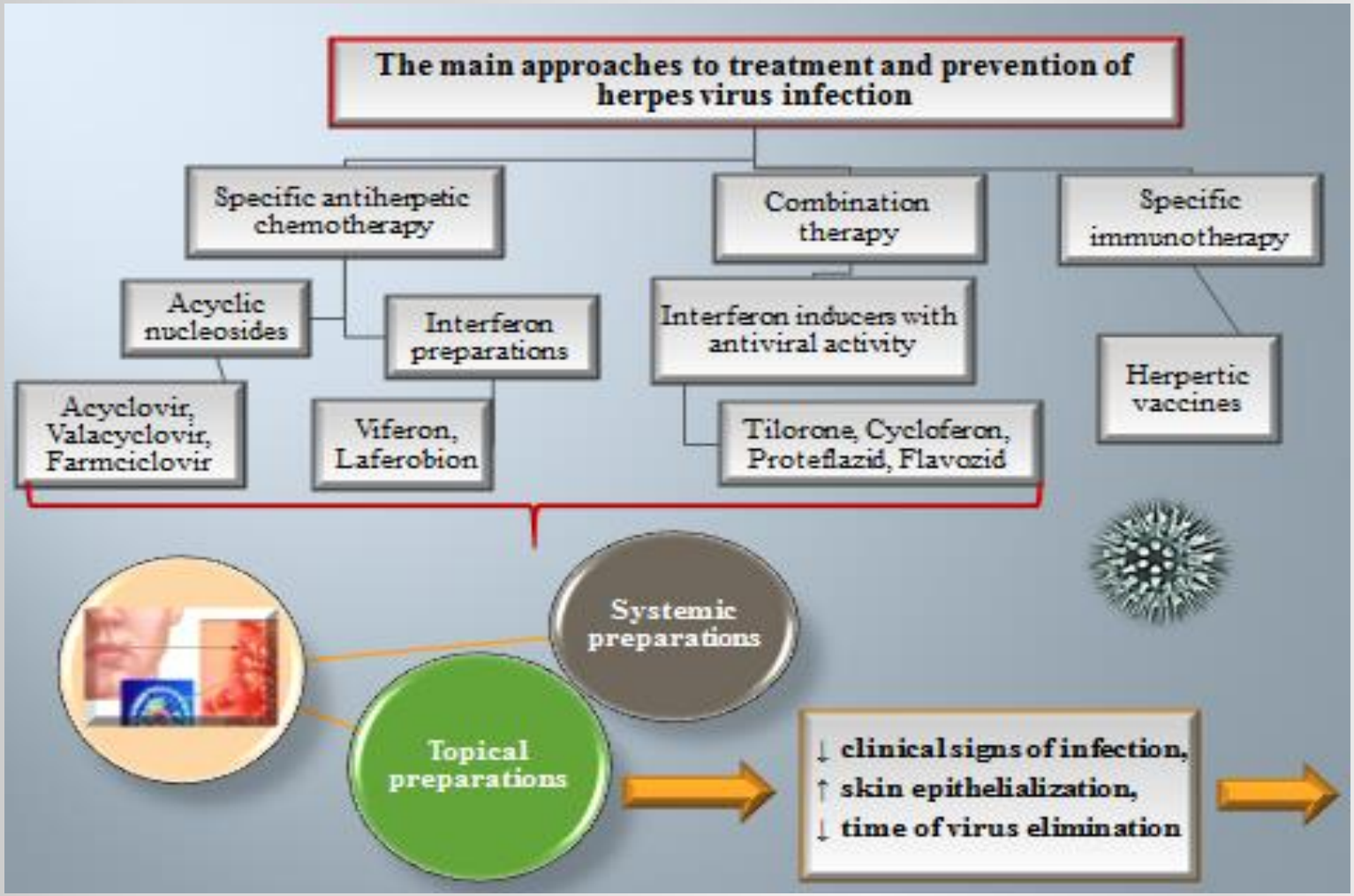
Investigation of Acute Toxicity of Tilorone Ointment for Topical Treatment of Herpes Virus Infection



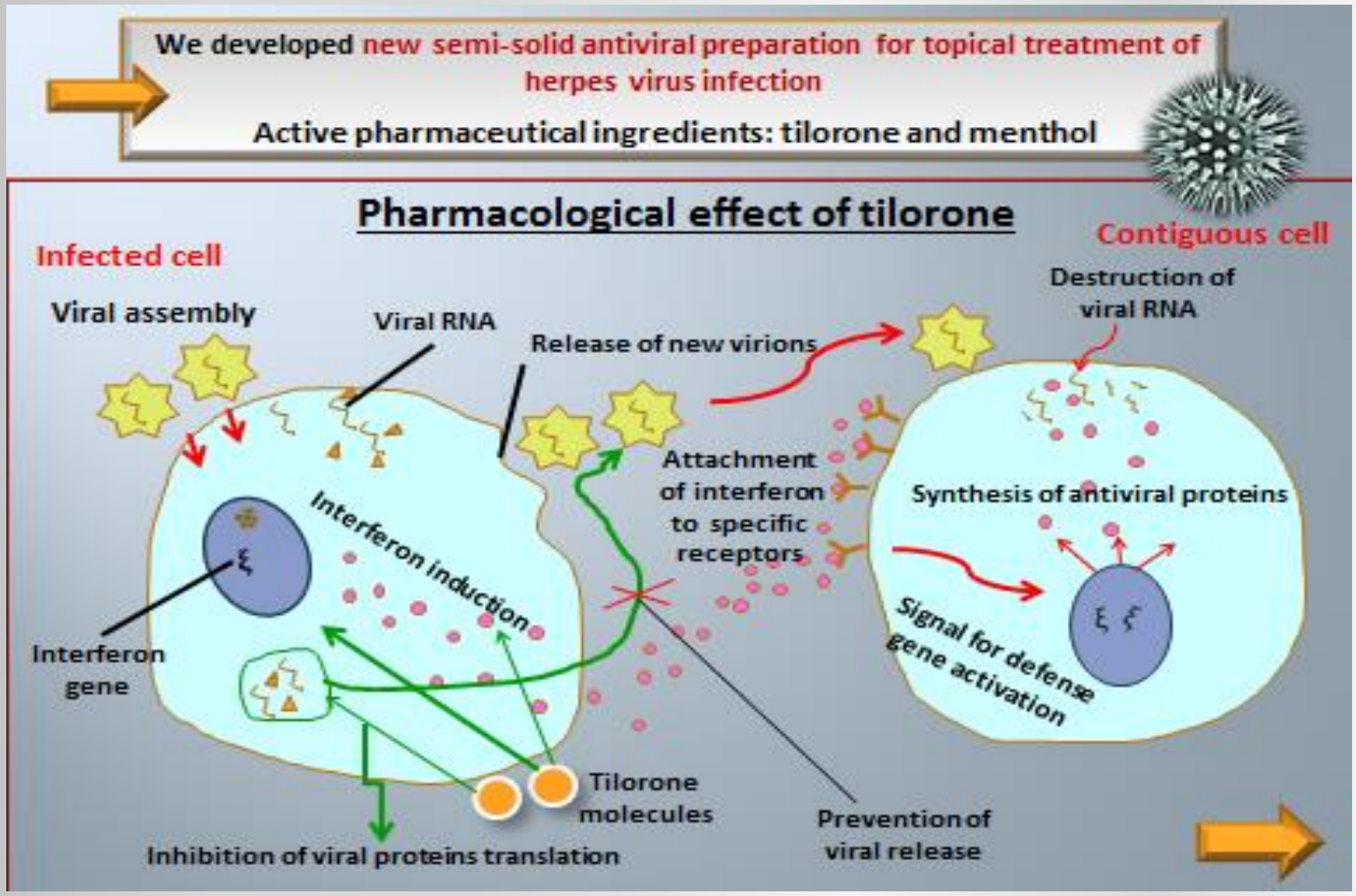
Abstract:
Tilorone (amixin) is a low molecular interferon inducer that is effective against a wide range of viral infections including herpes viruses. The mechanism of tilorone antiviral action is associated with inhibition of virus-specific peptides translation in infected cells resulting in the suppression of virus replication. An appropriate therapy of the viral infections with external rash besides the systemic preparations must include topical drugs. Considering this, we developed a new topical antiviral 2% tilorone preparation in the form of ointment.
The aim of investigation was to study the parameters of acute toxicity of the 2% tilorone ointment.
The acute toxicity of the ointment was studied by intragastric administration and cutaneous application. Acute intragastric toxicity was carried out in white outbred mice and white Vistar rats that were given intragastrically an aqueous solution of ointment at a dose of 0,5g/kg. Acute dermal toxicity was studied in white outbred mice. The animals were monitored daily for clinical signs in the course of 14 days.
It was determined that an effective dose of the 2% test ointment which does not cause toxic effects on human body is $DL_0 \leq 0,4$ g/kg. The results obtained enable us to attribute the developed drug product to the practically non-toxic.
Keywords: tilorone, ointment, acute toxicity.

Introduction:

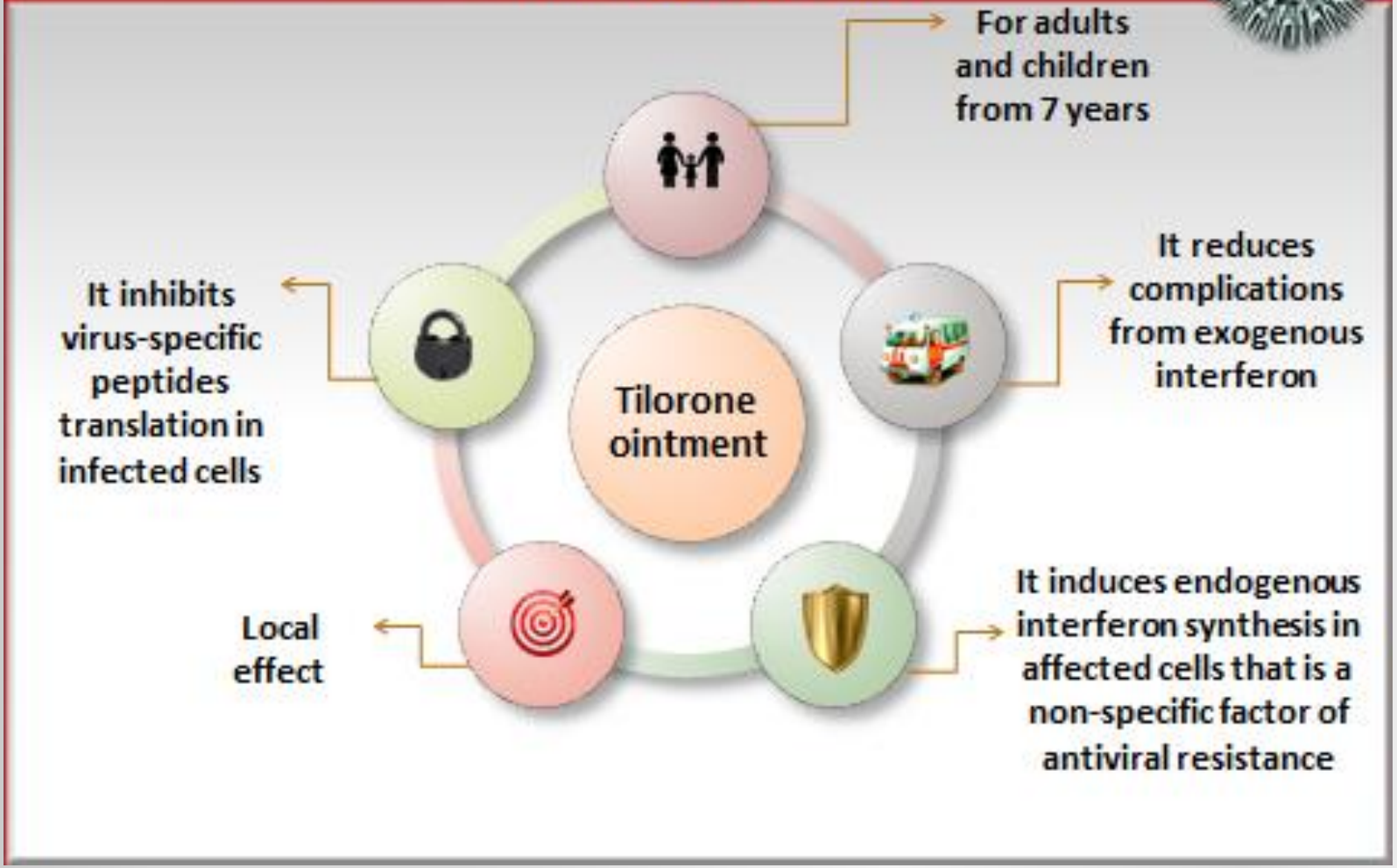


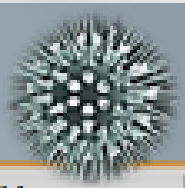
We developed new semi-solid antiviral preparation for topical treatment of herpes virus infection

Active pharmaceutical ingredients: tilorone and menthol



From previous results based on physical-chemical and biopharmaceutical tests, polyethylene oxide base was selected for the tilorone ointment





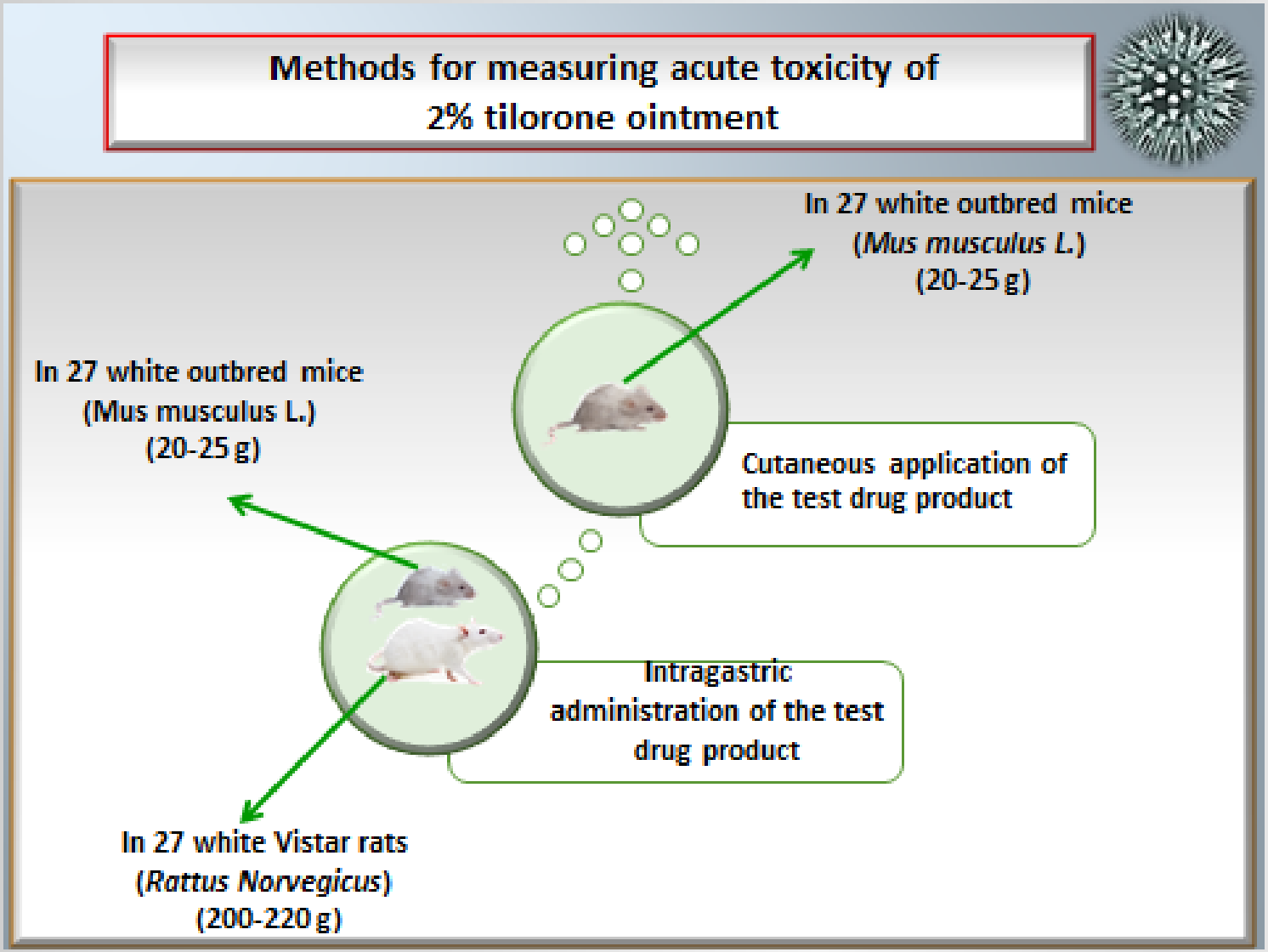
Ointments for topical treatment of herpes simplex virus infections are applied directly on the affected skin or mucous membranes.
Therefore those preparations are to be highly safe to minimize risk of complications.

The aim of investigation → to study the parameters of acute toxicity of the 2 % tilorone ointment

Investigations were performed in compliance with standards of humanitarian treatment with animals according to the European Convention for the Protection of Vertebrate Animals.

Selection of laboratory animals for studies was based on the requirements of International Council on Laboratory Animal Science, World Society for the Protection of Animals and Ukrainian instructive documents.

Results and discussion:



All animals were cared for humanely, in accordance with the European convention for the protection of vertebrate animals used for experimental and other scientific purposes [Council of Europe, Strasbourg, 2006].

Investigation of intragastric acute toxicity

v (tilorone ointment) = v(ointment base) = v(0,9% NaCl solution) = 5 mL (dose of tilorone – 0,5 g/kg)

White outbred mice

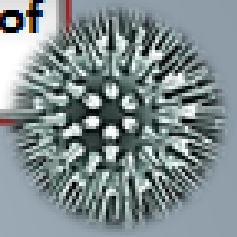
- Control intact animals (7) were given physiological solution per os ;
- Control animals (10) were given ointment base *per os*;
- Experimental animals (10) were given tilorone ointment per os.

White Vistar rats

- Control intact animals (7) were given physiological solution per os;
- Control animals (10) were given ointment base per os;
- Experimental animals (10) were given tilorone ointment per os.

Dose of tilorone for both species of rodents was the same

Results of investigation of the acute intragastric toxicity of 2% tilorone ointment



Single dosing of 2% tilorone ointment and ointment base did not cause the death of the experimental animals

Transient reactions of cardiovascular system, decrease of muscle tone and physical activity in the first 10-20 min after administration of preparations were related to stress response. Complications were not observed in the further days of the experiment

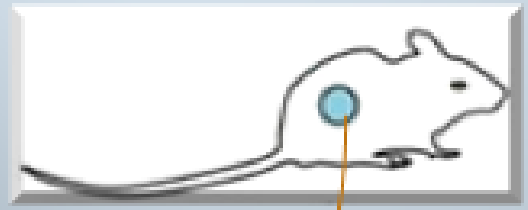
Differences in the weight dynamics between the control intact animals and other groups were not reported

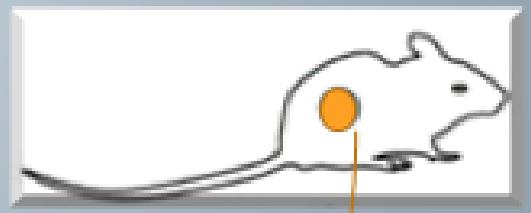
Peroral administration of 2% tilorone ointment at a dose of 0,5 g/kg (equivalent to tilorone) did not permit to determine the DL_{50} in the experiment

Dose of ointment – 0,5 g/kg (equivalent to tilorone) – has been accepted as an effective dose of the substance – DL_0

Investigation of acute dermal toxicity of 2% tilorone ointment

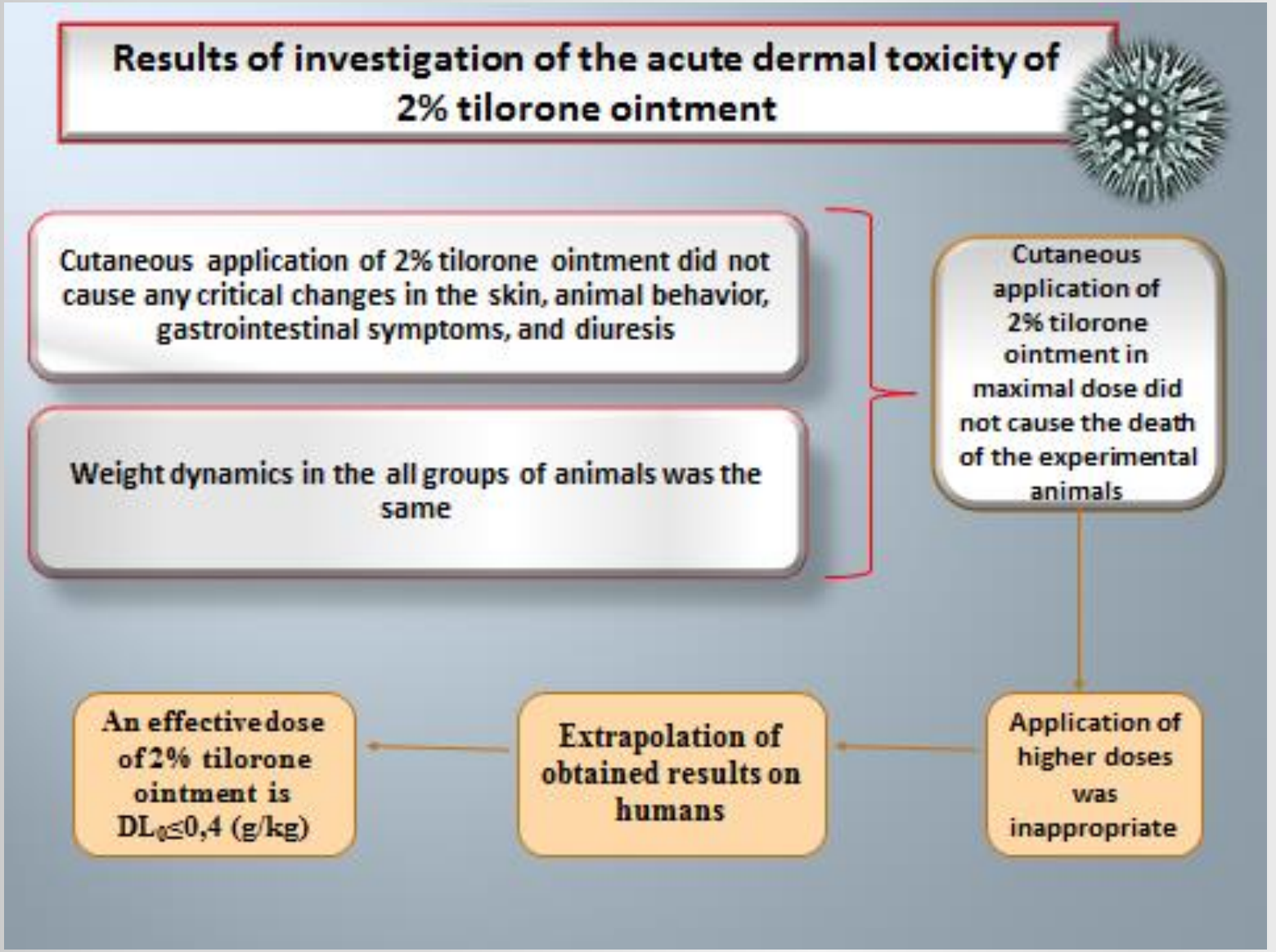
Control intact animals (7) were cutaneously applied with physiological solution	Control animals (10) were cutaneously applied with ointment base	Experimental animals (10) were cutaneously applied with 2% tilorone ointment



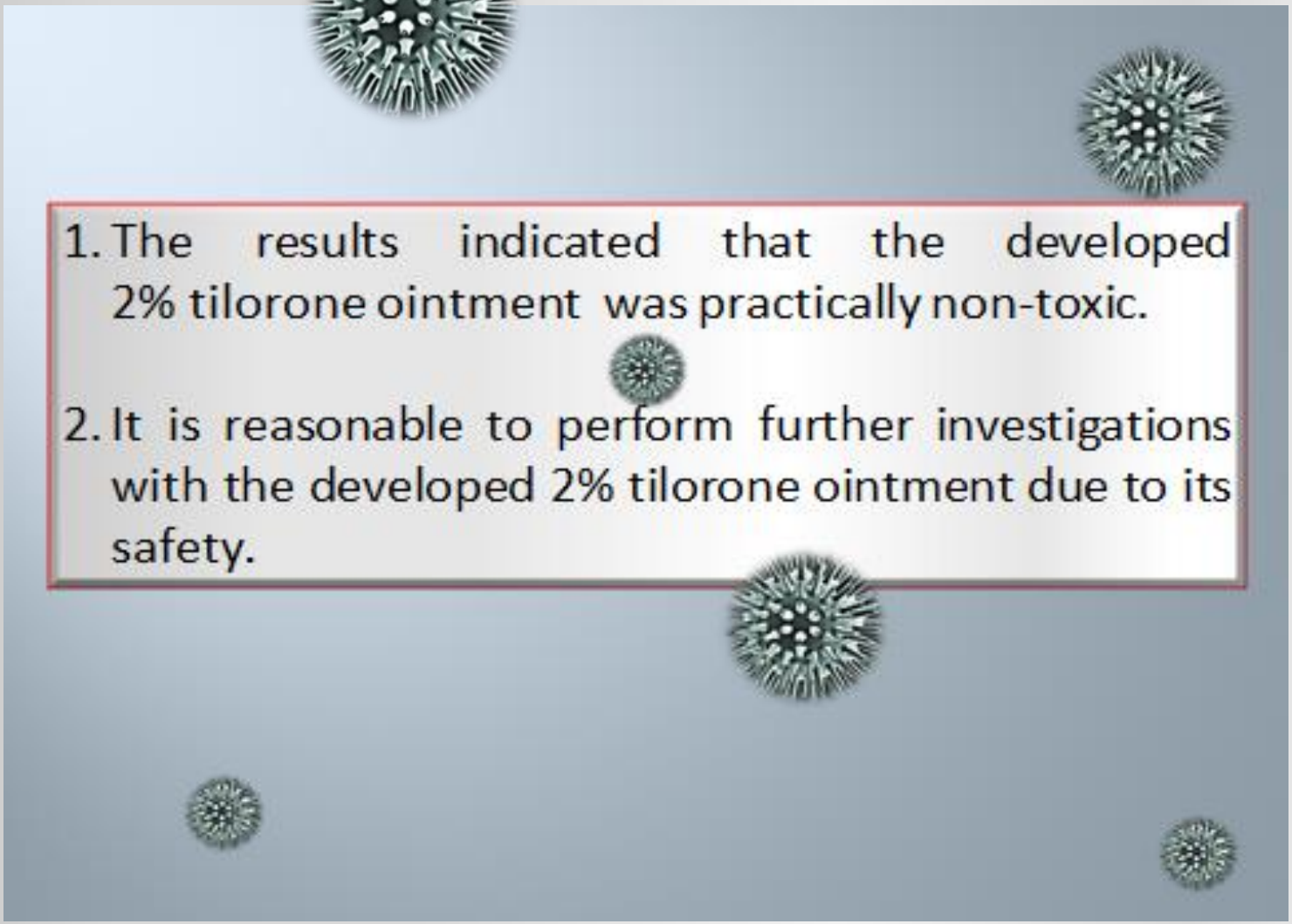


Application area was 5,5-6,0 cm^2 (10% of the body area)

Volumes of the ointment, the ointment base and the physiological solution were equal 0,35-0,4 mL (equivalent to 7-8 mg of tilorone for an animal or 350 mg/kg)


Results of investigation of the acute dermal toxicity of 2% tilorone ointment
Cutaneous application of 2% tilorone ointment did not cause any critical changes in the skin, animal behavior, gastrointestinal symptoms, and diuresis
Weight dynamics in the all groups of animals was the same
Cutaneous application of 2% tilorone ointment in maximal dose did not cause the death of the experimental animals
Application of higher doses was inappropriate
Extrapolation of obtained results on humans
An effective dose of 2% tilorone ointment is $DL_0 \leq 0,4$ (g/kg)

Conclusions:



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