



RESEARCH PAPER

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Evaluation of the specific pharmacological activity of *Padus grayana* Maxim dry extract on an experimental model of staphylococcal infection in mice

Murzabaeva Elvira Bolotbekovna¹, Shafee Ur Rehman^{*1}, Ismailov Isabek Zailidinovich², Kudaibergen Osmonaliev¹, Sabirova Tamara Semenovna³

¹Faculty of Medicine, Ala-Too International University, Bishkek, Kyrgyzstan

²Institute of Chemistry and Phytotechnology, National Academy of Science, Bishkek, Kyrgyzstan

³Faculty of Pharmacy, Kyrgyz State Medical Academy, Bishkek, Kyrgyzstan

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Abstract

Padus grayana Maxim belongs to the family Rosaceae and one of the important herbal plants. The extract of the plant is used to treat many diseases. Hence the current study was conducted to investigate the specific pharmacological activity of *Padus grayana* Maxim. The extract of the plant was obtained from the dried stem, leaves, and flowers of the plant. A series of experiments were conducted to study the effect of the phytoextract on the development of staphylococcal infection in 40 outbred white mice. The results show that prophylactic administration of the dry extract of *Padus grayana* Maxim to mice at a dose of 200 mg/kg of body weight led to a reduction in mortality by 60% and an improvement of the clinical symptoms of staphylococcal infection in mice. After one week of using the extract of *Padus grayana* maxim in infected mice, the survival rate of the experimental group was higher than the control group which was 80%, and normalization of hematological parameters of peripheral blood in infected animals was also finding significantly improved. Hence, we concluded that the extract of *Padus grayana* maxim has significant results in the enhancement of immunity against *Staphylococcus*.

* **Corresponding Author:** Shafee Ur Rehman ✉ shafeeur.rehman@alato.edu.kg

Introduction

Medicinal plants have a rich potential phenomenon of new compounds with a wide range of pharmacological activities (Gurib-Fakim, 2006). Systematic research in the field of herbal medicine has contributed to the fact that over the past decade, some herbal remedies with immunomodulatory effects have taken one of the leading places in clinical practice (Zhang *et al.*, 2023). It is also important that, having sufficient effectiveness, minimal risk of side effects, simplicity of use, herbal medicines have a relatively low cost, making this group of drugs economically affordable for most patients (Lee and Barnes, 2022; Santana *et al.*, 2024). WHO fully recognizes the importance of herbal medicines for the health of many peoples of the world, which is reflected in a number of decisions of the World Health Assembly (Tian *et al.*, 2024). Rosaceae, the rose family of flowering plants (order Rosales), composed of some 2,500 species in more than 90 genera (Kessler, 2022; Parnell, 2024). The family is primarily found in the North Temperate Zone and occurs in a wide variety of habitats (Jiang *et al.*, 2023).

Padus grayana Maxim belong to family Rosaceae and important plant used as an herbal medicine. The plant extract is used against many infectious diseases (Kadioğlu *et al.*, 2024). In clinical practice, immunomodulators are used for many diseases like acute respiratory infections of viral, bacterial and mixed nature; gastrointestinal diseases associated with microflora imbalance; autoimmune and allergic diseases, etc. (Ashique *et al.*, 2024; Shilpi *et al.*, 2024). The mechanisms of action of immunomodulators are diverse, some of them stimulate and activate the production of alpha and gamma interferons, which have antiviral and antitumor activity (Appiah *et al.*, 2024). In addition, IFN- γ is a pleiotropic interferon that regulates a huge range of immunological reactions (Solaymani-Mohammadi, 2024; Liang *et al.*, 2024). There is a particular interest of biologically active substances that have anti-inflammatory activity (Abd Razak *et al.*, 2024). This is due to the fact that excessive stimulation of the production of pro-inflammatory cytokines - interferons, IL-1, IL-

6, TNF- α , IL-10 can provoke a so-called “cytokine storm”, which results in the development of multiple organ failure syndrome leading to the death of the patient in the mildest period is just a few hours (Ramoni *et al.*, 2024). The pathogenesis of this syndrome includes a whole range of diseases: infectious-toxic shock, sepsis, acute pancreatitis, extensive burns and injuries, etc. (Ramoni *et al.*, 2024).

To treat the immunodeficiency conditions, various drugs both synthetic and natural origin are used among particular interest the herbal preparations, which compare favorably with synthetic drugs with a wide range of therapeutic effects, low toxicity and the associated possibility of long-term use (Choudhary and Verma, 2024; Bhattacharjee *et al.*, 2024), the search and development of which is one of the pressing problems of modern pharmacology. The purpose of this study was to evaluate the specific pharmacological activity of the dry extract of *Padus grayana* Maxim.

Materials and methods

The preclinical study of the dry extract of *Padus grayana* Maxim was carried out in accordance with the “Rules for the preclinical assessment of the safety of pharmacological agents (GLP)” (Sandeep *et al.*, 2024) and “Guidelines for conducting preclinical studies of drugs (Denny, 2024).

The plant material

The dry extract of *Padus grayana* Maxim (a species of bird cherry from the Rosaceae family), obtained by freeze-drying and stabilized with lactose monohydrate (1part lactose / 2 parts dry extract of *Padus grayana* Maxim) (Madi *et al.*, 2024). A solution of the plant substance was prepared by dissolving the required sample in purified water. If a suspension was formed, the solution was thoroughly shaken before administration. Based on the maximum permissible volumes of injected fluid per animal, the volume of injected substance was no more than 0.8 ml per mouse.

Animal models and experimental procedure

During the research, 80 outbred mice of both sexes were used in the experiment. The body weight of outbred mice at the beginning of the study was $20 \text{ g} \pm 10\%$. The study of the specific activity of the dry extract of *Padus grayana* Maxim was carried out in two steps. The first step of research included assessing the effect of *Padus grayana* Maxim dry extract on nonspecific resistance in mice. Here, the nonspecific immunostimulant activity of the studied phytoextract was studied in an infectious model. In this series of experiments, dry extract of *Padus grayana* Maxim was administered to experimental animals according to a prophylactic regimen.

The second step of research on the dry extract of *Padus grayana* Maxim was its use in the treatment of generalized staphylococcal infection in mice caused by a clinical isolate of *Staphylococcus aureus*. At the same time, the therapeutic anti-inflammatory effect was studied in a septic model. After using the extract of *Padus grayana* Maxim in

infected mice models. The efficiency of the drugs was further analysed by using hematology test. And the results were further analysed using statistical approach.

Results and discussion

Evaluation of the effect of dry extract of *Padus grayana* Maxim on nonspecific resistance in mice

In a series of experiments to study the effect of the phytoextract on the course of staphylococcal infection, 40 outbred white mice were used according to a preventive regimen. At the first stage of the experiment, 40 animals of all 4 groups were administered the phytoextract in doses of 10 mg/kg, 100 mg/kg and 200 mg/kg intragastrical for three days using a metal needle with olive oil. At the second stage of the experiment (on the 4th day), mice were infected with a clinical virulent isolate of *Staphylococcus aureus* at a dose of 1.5×10^9 CFU/individual by intraperitoneal injection of a suspension of the isolate in sterile water in a volume of 0.2 ml (Hao *et al.*, 2024).

Table 1. Effect of dry extract of *Padus grayana* Maxim on the course of staphylococcal infection in mice when administered according to a prophylactic regimen (n=10)

Group	24 hours of observation									
	1	2	3	4	5	6	7	8	9	10
Control	0/10	3/10	4/10	3/10	-	-	-	-	-	-
10 mg/kg	0/10	2/10	3/10	4/10	1/10	-	-	-	-	-
100 mg/kg	0/10	1/10	3/10	3/10	2/10	-	-	-	-	-
200 mg/kg	0/10	0/10	1/10	2/10	1/10	-	-	-	-	-

The animals were then observed for 10 days: mortality, changes in body weight, and clinical signs of the development of staphylococcal infection were noted. Analysis of the observation results showed that on the second day after infection, animals in the control group, as well as in animals that received the studied phytoextract in doses of 10 mg/kg and 100 mg/kg, had a pronounced pattern of development of the infectious process. Within 3-4 hours after infection, the animals became inactive, refused to eat, huddled together, slept most of the day, and their fur became grayish and disheveled. On days 2-6 of the experiment, the death of animals was observed (Table 1).

In the group of mice that received 200 mg/kg of the studied phytoextract, mortality was also observed, but

clinical signs of infection were much less: the mice ate food poorly, were inactive, and slept a lot. The studied phytoextract in doses of 10 mg/kg and 100 mg/kg did not have a significant effect on the mortality of experimental animals. By the end of 5 days, all animals of these groups died (Fig. 1).

Although the results of clinical observation revealed more smoothed symptoms of the development of staphylococcal infection in animals of these groups. In the group of animals receiving dry extract of *Padus grayana* Maxim at a dose of 200 mg/kg body weight, the mortality of mice was reduced by 60% compared to the control group. From the data presented in Table 1, it is clear that in the control and group 1 all animals died by the end of 4 days. The decrease in

body weight of mice in the group of animals receiving the studied phytoextract at a dose of 100 mg/kg on the 5th day of observation after infection was catastrophic and amounted to more than 30% of the initial values. By day 7, only one mouse in this group survived. Based on the principles of humanity, the mouse was killed on the same day by cervical dislocation.

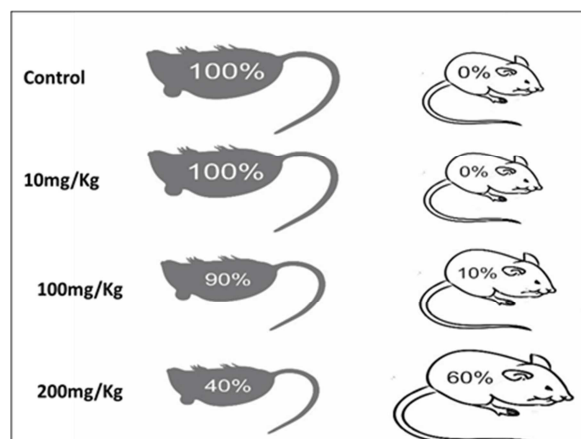


Fig. 1. Mortality of mice with staphylococcal infection when administered dry extract of *Padus grayana* Maxim according to the prophylactic regimen (n=10)

In the group of animals that received the studied phytoextract at a dose of 200 mg/kg, the decrease in body weight of mice on the 5th day of observation after infection was about 21% of the initial values. On

the 10th day of observation, the 6 surviving mice already had an increase in body weight from 15.9 ± 1.9 g to 17.2 ± 2.2 g, although not reaching the initial values (Table 2). The results obtained allow us to conclude that the prophylactic administration of the dry extract of *Padus grayana* Maxim to experimental animals at a dose of 200 mg/kg of body weight led to a reduction in mortality by 60% and an alleviation of the clinical symptoms of staphylococcal infection in mice, which was the rationale for continuing the study of the therapeutic activity of the studied phytoextract.

Evaluation of the anti-inflammatory activity of *Padus grayana* Maxim dry extract against generalized staphylococcal infection in mice. Infections caused by staphylococcus in humans are often accompanied by an acute systemic inflammatory reaction with high mortality (Liu *et al.*, 2024). One of the convenient and well-studied experimental models of pathological conditions is bacteremia in mice caused by intravenous administration of a virulent strain of *S. aureus*. When using this model pathology, a wide range of reactions and clinical signs are observed in experimental animals. Among certain prognostic interest are leukocytosis or leukopenia, as well as the production of proinflammatory cytokines - TNF- α , IL-6, C-reactive protein (He *et al.*, 2024).

Table 2. Dynamics of body weight of mice with staphylococcal infection when administered dry extract of *Padus grayana* Maxim according to the preventive regimen (n=10)

Group	24 hours of observation			
	3 days before infection	On the day of infection	5	10
Control	20,1 \pm 1,2	20,2 \pm 1,1	-	-
10 mg/kg	19,8 \pm 0,9	19,5 \pm 1,2	-	-
100 mg/kg	20,8 \pm 1,3	20,2 \pm 0,8	14,4 \pm 2,1	-
200 mg/kg	20,3 \pm 1,4	20,5 \pm 1,2	15,9 \pm 1,9	17,2 \pm 2,2

A strong inflammatory reaction and a “cytokine storm” play a leading role in the pathogenesis of septic infections. The main indicators of the clinical manifestation of sepsis in laboratory animals are: decreased activity and appetite, and, as a consequence, body weight, changes in the leukocyte formula, the presence of septic foci in parenchymal organs and the presence of a pathogen in the blood (septicopyemia). To obtain a

septic model, the Guidelines for Experimental (Preclinical) Study of new biological active substances, recommend the use of a virulent strain of *Staphylococcus aureus* isolated from patients (Tirant *et al.*, 2024). Before we start the main experiment, an infectious dose of *S. aureus* was preliminarily established at a concentration of 12×10^9 CFU/ml, which caused the death of 90% of mice by 7 days from the moment of infection.

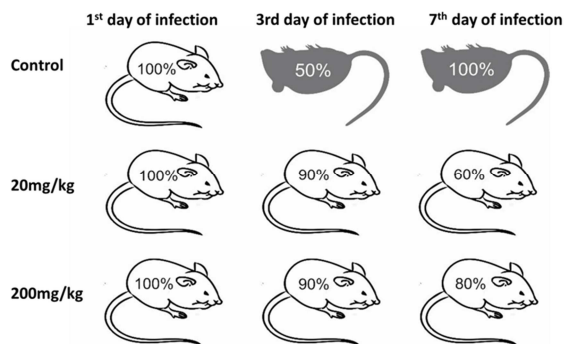


Fig. 2. Survival of mice with staphylococcal infection when administered dry extract of *Padus grayana* Maxim according to the treatment regimen (n=10)

In a series of experiments to study the effect of the phytoextract on the course of staphylococcal infection when applied according to a therapeutic regimen, 40 outbred white mice were used. Animals were infected by a single injection into the tail vein of mice with 0.2 ml of a suspension of *Staphylococcus aureus* in a 0.9% sterile solution of sodium chloride. The effectiveness of reproducing the infectious process in experimental animals was confirmed by the presence

of clinical symptoms and a significant decrease in the body weight of mice by 1.2 times 3 days after infection. On the 4th day after the development of a generalized staphylococcal infection, mice were started to receive a solution of dry extract of *Padus grayana* Maxim in doses of 20 mg/kg and 200 mg/mg for 7 days.

Infected but untreated animals served as controls. Infected and untreated animals began to die already on the 3rd day of the experiment. By the 7th day of observation, all animals in this group died. At the same time, in groups of animals that received the studied phytoextract, mortality decreased and life expectancy increased. Thus, in the group of animals that received the phytoextract at a dose of 20 mg/kg, by the 7th day of the experiment, mortality reached 40%. In mice that received a solution of dry extract of *Padus grayana* Maxim according to a treatment regimen at a dose of 200 mg/kg body weight, the survival rate of mice by the 7th day of the experiment was already 80% (Fig. 2).

Table 3. Hematological parameters of female mice with reproduced staphylococcal infection after administration of a solution of dry extract of *Padus grayana* Maxim for 7 days

Index	Control group (n=10)	Dry extract of <i>Padus grayana</i> 20 mg/kg (n=10)	Dry extract of <i>Padus grayana</i> 200 mg/kg (n=10)
RBC	10,2±1,3	8,4±0,1	10,5±1,3
Leukocytes	4,5±1,4	8,45±1,8	5,5±0,8
Lymphocytes	3,7±1,5	5,5±0,4	4,6±0,6
Granulocytes	2,2±0,6	1,45±0,40	1,6±0,5
Monocytes	1,05±0,40	2,6±0,1**	1,0±0,4
Platelets	1041,0±59,0	552,5±137,9*	965,5±138,0

* p<0,05, ** p < 0,01

Table 4. Hematological parameters of male mice with reproduced staphylococcal infection after administration of a solution of dry extract of *Padus grayana* Maxim for 7 days

Index	Normal (n=10)	Dry extract of <i>Padus grayana</i> 20 mg/kg (n=10)	Dry extract of <i>Padus grayana</i> 200 mg/kg (n=10)
RBC	10,58±1,0	9,05±1,6	10,4±1,7
Leukocytes	4,52±1,3	12,2±0,4**	4,9±1,2
Lymphocytes	2,82±1,0	5,3±0,8	5,0±1,6
Granulocytes	2,86±0,6	1,85±0,60	1,9±0,7
Monocytes	1,18±0,4	2,45±0,4	1,4±0,3
Platelets	1005,4±110,0	654,0±185,3	892,3±117,8

** p<0,01

After the mice were infected, their body weight began to rapidly decline. Appetite worsened, animals refused food and water. The body weight of mice by

day 3 in all groups of infected animals was significantly lower than that of control animals. By the 7th day of therapy with the studied phytoextract,

in mice receiving the studied substance at a dose of 20 mg/kg, body weight increased by 18.8%, and in the group of animals receiving dry extract of *Padus grayana* Maxim at a dose of 200 mg/kg, a significant increase in body weight was observed.

Consequently, a study of the dynamics of body weight in mice revealed a direct dependence of body weight on the applied dose of *Padus grayana* Maxim dry extract. Hematological changes in septic infections have great prognostic significance. Leukocytosis (more than $12 \times 10^9/l$) or leukopenia (less than $4 \times 10^9/l$) with neutrophilia is one of the criteria for systemic inflammatory response syndrome (SIRS). After administering the dry extract of *Padus grayana* Maxim to infected animals at a dose of 20 mg/kg, monocytosis and thrombocytopenia were observed in females. However, other indicators did not differ significantly from the indicators of animals in the control group (Table 3).

In males there was a significant increase in the number of leukocytes ($p < 0.01$), but without a shift in the leukocyte shape to the left or right. This suggests that the period of the acute phase of development of the infectious process has passed, and the formation of a protective reaction of the body is observed, aimed at neutralizing the microbe, as well as restoring homeostasis (Table 4).

In infected animals that received dry extract of *Padus grayana* Maxim at a dose of 200 mg/kg for 7 days according to the treatment regimen, all hematological parameters reached values that differed little from those of animals in the control group. Normalization of the number of leukocytes and restoration of platelet levels in infected animals receiving the studied phytoextract at a dose of 200 mg/kg is the most important positive sign in systemic inflammatory response syndrome, when dysfunction of many organs and systems of the body is observed (Ntwali *et al.*, 2024). The results obtained were consistent with the available literature data, according to which many polyphenolic compounds contained in phytoextracts have pronounced anti-

inflammatory and immunostimulating activity. They suppress the secretion of proinflammatory cytokines IL-1, TNF- α and enhance phagocytosis (Neudorf *et al.*, 2024; He *et al.*, 2024). One of the biologically active substances of the studied phytoextract is chlorogenic acid. There is evidence in the literature that chlorogenic acid increases the survival of mice with staphylococcal infection, but the contamination of internal organs remains (Chen *et al.*, 2024). Necropsy of animals, carried out on the 8th day of the experiment, and showed the persistence of foci of the infectious process in the lungs and kidneys in all groups of infected animals. Moreover, these lesions were least pronounced in animals that received the studied phytoextract at a dose of 200 mg/kg.

Conclusion

In our study the dry extract of *Padus grayana* Maxim dose-dependently suppresses the hyperinflammatory response during septic staphylococcal infection in experimental animals. When the dry extract of *Padus grayana* Maxim is administered according to the treatment regimen, the survival rate of mice increases to 80%, and peripheral blood parameters are normalized. Using an experimental septic model in mice induced by a clinical isolate of *Staphylococcus aureus*, it was found that the dry extract of *Padus grayana* Maxim has an immunomodulatory effect. Hence, we concluded from the experimental analysis that the extract of *Padus grayana* Maxim could be a significant immunomodulator.

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