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Pharmaco-Toxicological Assessment of a New Phytopreparation and its use in Calf Dyspepsia

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ABSTRACT

The work aimed to create dosage forms (infusion, extracts) from walnut leaves and bark, to experimentally study their toxicity, and use them to treat dyspepsia in calves. The study was based on observation, statistical analysis, and scientific experiments. The experiments were conducted with the division of calves into experimental and control groups. Laboratory tests included hematological and biochemical analysis. The experiments simulated pathological processes in animals in the vivarium of the Kazakh National Agrarian University and farms of Kazakhstan. The effectiveness of the preparation for activating the immune system was confirmed, and the dosage and method of use were determined. Regarding toxicological methods, general and special types of toxicity were used. According to the developed methodology, alcoholic and aqueous extracts and infusion from the medicinal plant collection were produced. The study developed a liquid phytopreparation derived from walnut (*Juglans regia* L.) containing bioactive compounds such as tannins, flavonoids, and essential micronutrients. The preparation was proven low-toxic (hazard class IV) with no significant adverse effects. Its application significantly reduced recovery time and normalized blood parameters in calves with dyspepsia, improving therapeutic effectiveness by 20–25% and reducing mortality by 30%. The findings offer a sustainable alternative to antibiotics, enhancing the health and safety of newborn calves in livestock farming.

Key words: Medicinal raw materials, Extract, Cumulation, Toxicity, Clinical status.

INTRODUCTION

The most acute problem for dairy farms in the breeding and rearing of cattle is the high incidence of dyspepsia in newborn calves. In calves received from young heifers, this gastrointestinal tract disease reaches an average of 83-100% at farms (Korotkiy et al. 2024).

Livestock production growth is inextricably linked introducing advanced technologies for keeping and caring for animals, increasing their fertility, and improving breeding work. An important goal is the preservation of newborn calves and the cultivation of young animals that are healthy, well-developed, and adapted to industrial keeping. These calves form the basis for increasing the yield of livestock products (Barinov et al. 2006; Harish 2017).

The analysis of cattle morbidity structure in Kazakhstan farms shows that diseases in young animals affect all animal-breeding regions.

Every year, 70% of newborn calves suffer from diseases with a general syndrome of acute dysfunction of the digestive system, mainly in the early neonatal period of development (Praveen Kumar et al. 2010). Due to its extreme importance in the pathology of cattle, calf dyspepsia remains an urgent topic for scientific studies, accumulating achievements in veterinary medicine and related fields. The work of many veterinary specialists focuses on controlling the massive incidence of gastroenteritis in calves in the neonatal period (Saha and Paul 2012). The screening and evaluation of effective therapeutic and prophylactic agents are ongoing to identify better solutions for managing and preventing diseases. However, despite the increasing number of promising biological and chemotherapeutic preparations introduced into veterinary practice, the susceptibility to diseases in young cattle remains high (Kamalieva et al. 2020).

The organization and technology of raising calves should be competently based on the physiological processes of their individual development and contribute to the formation of animals with good body resistance, long duration of economic use, and high milk productivity (Mpofu et al. 2022; Akhazhanov et al. 2023). To obtain and

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raise healthy calves, Russian and Kazakh scientists and practitioners developed a set of progressive, cost-effective veterinary organizational and economic measures that can be applied to each dairy farm and complex (Bakhtina 2003; Zhaxalykov et al. 2024).

Dyspepsia in newborn calves in the first 10 days of life, as evidenced by our long-term observations on most farms, is mainly accompanied by digestive disorders, diarrhea, severe emaciation, hypogammaglobulinemia, metabolic disorders, intoxication, growth retardation, and delayed development (Blokhin et al. 2011).

The further development of animal husbandry depends on several key factors. Ensuring the stable well-being of farms requires reducing morbidity rates among livestock. It is also essential to improve the efficiency of veterinary services. Expanding and strengthening the material and technical base of veterinary services is critical. Moreover, livestock enterprises must be adequately supplied with necessary pharmacological agents. These agents should be available in sufficient quantities, offered in diverse assortments, and provided in convenient forms with high therapeutic effectiveness (Sivkova and Domatskiy 2023). It is necessary to solve the issues of veterinary care of industrial-type livestock farms in a new way and equip them with healthy livestock. This obliges veterinary specialists to increase the level of organization of veterinary business, paying special attention to preventive, antiepizootic, veterinary, and sanitary measures and prevention of infectious and non-communicable diseases.

Dyspepsia pathogenesis is complex and diverse. Therefore, comprehensive treatment requires a significant set of modern medicines. Traditional methods of treating bronchopneumonia are often ineffective, which leads to a prolonged recovery period. Therefore, the inclusion of natural preparations with a wide spectrum of action in traditional therapy can be justified from a medical point of view (Ramasubramaniaraja 2011; Amiri et al. 2023; Smolovskaya et al. 2023). Their advantage in comparison with many synthetic products is that they contain biological activators of metabolic processes that act in a complex way (Lokireddy et al. 2013). Natural preparations also usually have mild effects and minimal side effects and complications. Biologically active components of herbal remedies are more closely related to the animal body than synthetic preparations (Meshcheryakov and Trubnikova 2002; Wampah et al. 2024).

Based on this, the search for new herbal remedies for the treatment of dyspepsia in calves remains relevant.

Veterinary medicine has a large arsenal of medicines and methods of treating digestive diseases. However, in most cases, these measures are reduced to antibacterial agents (Mussayeva et al. 2021). Excessive and irrational use of antibiotics is accompanied by increased resistance of microorganisms and fungi (Trubnikova 2002; Armansyah et al. 2023), development of toxic reactions (Meshcheryakov and Trubnikova 2003a), suppression of the humoral and cellular factors of the immune system (Trubnikova 2003a) and disruption of vitamin metabolism (Meshcheryakov and Trubnikova 2003b; Nagati et al. 2021).

The way out of this situation is the synthesis of new chemotherapeutic agents with pronounced antibacterial activity, the use of complex preparations, or the search for natural remedies, including herbal remedies with high therapeutic efficacy and no side effects (Trubnikova 2003c; Korotkiy et al. 2024).

This served as the basis for choosing the research topic. Research papers show that in the pathology of the gastrointestinal tract in calves, the role of component complexes in preparations recommended for pathogenetic therapy of this disease should not be overestimated (Gull 2022; Gerceva et al. 2023; Kalinkina et al. 2023; Reshetnikova et al. 2024). This also applies to biological probiotics, widely used in gastrointestinal pathology control in newborn calves. Probiotics are indispensable therapeutic and prophylactic agents, as part of their main function in the complex of pathogenetic therapy, i.e., normalization of intestinal microflora. However, due to the variety of causes of dyspepsia in calves and immunological causes, the therapeutic use of these preparations in production conditions does not always lead to stable results (Trubnikova 2003b).

The potential of existing non-preparation treatments, namely phytopreparation therapy for acute functional pathology of the gastrointestinal tract in productive animals, has not been studied in veterinary medicine for commercialization point of view.

Nuts, by their nutritional value, can be attributed to natural biological concentrates. With a low moisture content, nuts have a unique complex of micro and macronutrients. Since ancient times, it has been believed that nuts activate physical and mental activity, promote longevity, and provide energy balance in the human body. The dissemination of new research results on the benefits of nuts obtained at leading world universities contributes to an increase in nut consumption (Tapsell et al. 2023; Mandalari et al. 2023). The international nut production and processing industry has been actively developing in recent decades and is characterized by the highest growth rates compared to other types of agro-industrial business. Over the past 10 years, global nut production has increased by almost 40%, and sales volumes have increased by 116%. A particularly sharp jump in demand was established for walnuts as the most important alternative source of the main physiologically active compounds replacing animal food (Dratwa-Chalupnik et al. 2012). Researchers have found that walnuts contain the highest content of polyunsaturated fatty acids compared to other nuts. Walnuts also contain a large amount of antioxidants, polyphenols and other biologically active substances (Zhylgeldieva et al. 2018). The walnut tree and its processed products (leaves and fruits) contain fat (15%), carbon (30g/kg), lysine (3.0%), multi-enzyme complex (1.5%), calcium (26.0%), phosphorus (8.2%), sulfur (24g/kg), magnesium (35mg/kg), zinc (950mg/kg), copper (158mg/kg), manganese (13mg/kg), cobalt (44mg/kg), iodine (38mg/kg), mercury (0.9mg/kg), vitamin A (400,000IU), vitamin D3 (200,000IU), vitamin E (200mg/kg), phospholipids (at least 5%), and essential oils (Busch et al. 2004; Dratwa-Chalupnik et al. 2012; Cho et al. 2013). These minerals are necessary for human and animal life (Cho et al. 2013; Sultana et al. 2022).

The purposeful use of new, promising phytopreparation requires morpho-functional and biochemical analysis of animal organs. The reaction of calves to pathological changes when medicinal plants are

used against digestive diseases is an important element in assessing structural changes. The use of walnut tincture or decoction in the dyspepsia of young animals was studied since 2020 by researches from the Kazakh National Agrarian Research University, located in Almaty, Kazakhstan.

The work aimed to manufacture dosage forms (infusion, extracts) from walnut leaves and bark and experimentally study their toxicity and their use in calf dyspepsia.

MATERIALS AND METHODS

Ethical approval

The study was conducted in accordance with the recommendations for animal experiments outlined by the International Council for Laboratory Animal Science (ICLAS, 2024).

Methods

The study was based on methods of direct observation, statistical analysis, and scientific experiments. The experiments were conducted following the experimental planning methodology by forming experimental (EG) and control (CG) groups of calves depending on the set goals.

Laboratory and clinical studies of animals involving hematological and biochemical analysis were performed using modern computerized equipment and test systems. The methodological approaches were implemented considering the relevance of the problem under consideration, based on which the main goal and objectives were determined and adequate techniques and available research methods were used.

The study was based on the experimental data obtained by artificially reproducing various models of pathological processes on laboratory animals in the vivarium of the Kazakh National Agrarian Research University (KazNAIU) and the results of treatment of young cattle with dyspepsia in farms in Kazakhstan.

Having determined the cost of the walnut selected for manufacturing the medicinal product, we performed its collection, preparation, and drying using generally accepted methods, including air-drying in shaded areas for 5–7 days, followed by crushing the dried materials into uniform pieces (1–1.5cm) to ensure optimal extraction quality.

Equipment

The equipment used in the study: hematology analyzer, distiller, electric water distiller, redistiller, electric laboratory scales, fume hood, electric calorimeter, PH meter, centrifuge, and thermostat (Blum 2006).

Location

To reach the set goals and objectives, the main research work was conducted in the research laboratory of the Department, the Kazakh-Japanese Innovation Center at KazNAIU, the Biochemical and Immunological Laboratory of the University of Warmia and Mazury (Poland), in the clinical and diagnostic laboratories of Almaty, scientific and production experiments in the veterinary clinic of KazNAIU and business entities of the Almaty and Turkestan regions.

Course of the study

1) In the farms of the Almaty and Turkestan regions, the prevalence of digestive diseases in calves and disease etiology and pathogenesis were studied. The technology of raw material preparation, drying, storage, and manufacture of medicines was conducted according to the methods described by (Turishchev 2007; Seifulla et al. 2018).
2) Pharmacological properties and preclinical studies of the phytopreparation were conducted based on the methods developed by Khabriev (2005) and Imran et al. (2014) on laboratory animals (guinea pigs, white mice, frogs, rabbits) in the KazNAIU veterinary clinic.
3) Hematological blood tests (red blood cells, hemoglobin, white blood cells, leukoformula) were conducted at the educational and scientific diagnostic laboratory using an MS 4/5 automatic analyzer (France).
4) The amount of total protein, protein fractions, alanine aminotransferase (ALT), and aspartate transaminase (AST) were determined using the Infrapid-61 comparative near-infrared spectroanalyzer at the CompactDualMini horizontal electrophoresis chamber (Belgium), and Agilent Technologies 6850 gas chromatograph.
5) Immunoglobulins (Ig) were identified to study the immune status of animals.

Prevalence of digestive diseases in calves

The incidence of dyspepsia in calves of the early neonatal period was studied in a large livestock region of the southeast of Kazakhstan, namely, in farms of the Almaty and Turkestan regions and an inter-regional veterinary laboratory. The analytical basis for the study was the materials of veterinary statistics from the regional veterinary department. This included information from the reports of the veterinary service of the state veterinary network for 2021-2023. Additionally, the study used the results of their observation (monitoring) of the neonatal dyspepsia situation in calves across four farms in different districts. Alieva Salima individual entrepreneur (IE) in the Almaty region, and farms in the Arys district of the Turkestan region). The diagnosis of dyspepsia in calves of the colostrum period was made comprehensively, considering the results of clinical, pathoanatomic and laboratory microbiological studies of material from newborn calves with acute gastroenteric insufficiency.

Monitoring was conducted according to a combination of factors recognized by the etiology of gastrointestinal pathology in calves of the colostrum period (Shcherbakov 2021). Emphasis was put on the alimentary deficiency factor, in particular, on the inferiority of colostrum in maternal cows as the root cause of neonatal gastroenteritis in calves (Shulga et al. 2012). Therefore, farms were evaluated according to indicators of compliance with veterinary and sanitary standards that determine the health of newborn calves, the quality of the feed base and rations for the main groups of breeding stock, types of feeding of dry and newly calved cows, conditions of keeping and feeding of newborn calves, sanitary and hygienic condition of calving pens, prophylactorium calf houses and equipment for colostrum feeding, with the definition of the coli-index. Colostrum quality indicators were determined in cows that had calves with dyspepsia that occurred in the early neonatal period of their development. Morning milk colostrum was taken

for the study in groups of mother cows (n=10) that had sick calves, each of which corresponded to the clinical form of neonatal gastroenteritis in their calves (mild and severe). Colostrum was tested for Turner acidity, total protein, albumins, globulins, calcium, phosphorus, carotene, and vitamin A. The metabolic status of cows from herds with an unfavorable status was tested selectively. In calved cows, testing was conducted on the biochemical parameters of blood serum, such as total protein, acid capacity, carotene, calcium, and phosphorus.

Phytopreparations

The phytopreparation was obtained from walnut leaves. Plant raw materials were collected considering the phases of vegetation and generally accepted recommendations for their harvesting. The harvested raw materials were dried in a shaded place. After 5-7 days, the raw material was crushed to 1-1.5cm. The crushed raw materials were put into a flat-bottomed flask made of heat-resistant glass, and a Liebig reverse refrigerator was attached to it, after which the flask with the raw materials was fixed with a holder above the heat source at an acute angle at a height of 0.5-1.2cm. The flask with the raw material was heated to a temperature of 100-110°C while it was simultaneously cooled. As a result of the above thermal reactions, a vapor-gas mixture was formed upon cooling of which condensate was obtained. The light condensate fraction was separated and moved to another container. The isolated fractions were mixed separately in a pepsin-acid mixture in a ratio of 1:3 and kept at a temperature of 38-39°C in a thermostat for 3 weeks. The resulting mixture was filtered and stored in the refrigerator (Dratwa-Chalupnik et al. 2012; Cho et al. 2013).

When studying the qualitative composition of the decoction, alkaloids, organic acids, terpene-type substances and 16 macro- and micronutrients were isolated. When studying the elemental composition of the phytopreparation (Table 1), the presence of about 16 macro and micronutrients in its composition was established and determined by using the atomic absorption spectrometer.

To work safely with new pharmacological agents, it is necessary to have information about their toxicity, possible ways of poisoning and other properties. The main criterion of the new preparations is their toxic effect on warm-blooded animals. In the first series of experiments, the acute toxicity of the components was determined upon their intragastric administration.

Determination of the toxicity of phytopreparations

For this purpose, we used non-linear intact females and males of mongrel white mice with an initial body weight of 18-22g, previously quarantined for two weeks in the vivarium of the KazNAIU. A total of 20 mice were used, distributed into 2 groups of 10 animals each. The animals were included in the groups considering their equal distribution according to gender. The first EG received a walnut infusion, and the second served as a CG and received distilled water (Table 2). To inject the components of the preparation, a 1-1-10:100 reusable injection syringe was used, to which a special olive-tipped needle was attached. The biological effect of the phytopreparation on the body of laboratory mice was evaluated considering their clinical condition and responses after a single dose. The duration of the experiment was 14 days, after which they were euthanized under ether anesthesia to assess the condition of internal organs.

Table 1: Elemental composition of the walnut phytopreparation

Indicator (element)	Unit of measurement	Quantity
Macronutrients		
Potassium	mg/100mL	70.1
Calcium	mg/100mL	20.0
Magnesium	mg/100mL	1.2
Sodium	mg/100mL	76.0
Micronutrients		
Mercury	mg/100mL	0.23
Iron	mg/100mL	0.5
Cadmium	mg/100mL	0.0002
Manganese	mg/100mL	0.091
Copper	mg/100mL	0.59
Molybdenum	mg/100mL	less than 0.001
Lead	mg/100mL	0.075
Zinc	mg/100mL	0.19
Cobalt	mg/100mL	0.5
Nickel	mg/100mL	0.148
Chrome	mg/100mL	0.26

Experiments on calves

The possibility of using the phytopreparation for calf dyspepsia was studied in four series of experiments on farms in Kazakhstan. These experiments were conducted on young cattle with an initial body weight of 48.5±2.1kg. In this experiment, 30 calves, under the age of 60 days and an average live weight of 48.5±2.1kg were used. The animals were divided into three groups of 10 animals each: CG, EG, and intact. The keeping and feeding conditions for calves of all groups were of the same type. For the adaptation of animals, the experiment began 2 days after the formation of animal groups.

Oxytetracycline 20% was administered intramuscularly once to calves of the first CG at a dose of 1mL/10kg of animal weight (20mg oxytetracycline dihydrate per 1kg of animal weight), 1 time per day. The second injection was conducted after 72 hours. Animals of the EG were given the walnut decoction in a dose of 300mL per animal parenterally, 1 time per day, for three days.

Table 2: Experiment design to determine the acute toxicity of the phytopreparation when administered per os to mongrel white mice (n=10)

Group	Tested component	Sex of the animal	Number of animals	Method of introduction	Dose, mL
1: experimental	Walnut leaves infusion	Male	5	Per os	0.5
		Female	5	Per os	0.5
Control	Distilled water	Male	5	Per os	0.5
		Female	5	Per os	0.5

For a more objective assessment of the general condition of calves, when the phytopreparation was included in the treatment regimen, hematological blood parameters were studied on the first day of the experiment, and then on the 7th and 11th days after the start of the experiment. The indicators of the hematological status of clinically healthy calves (the intact group) were regarded as the norm.

For a comparative assessment of therapeutic measures against dyspepsia in calves in the early postnatal period, two groups of animals from the EG were formed and given the decoction daily from the first day of life at a dose of 250-300mL per day. The CG consisted of animals treated according to the scheme used in the farm.

Ig determination

Determination of the M class Ig. In a measuring flask per 1 liter, 0.28g of veronal, 0.21g of medinal, and 0.024g of zinc sulfate were dissolved in redistilled water. Before the final solution was brought to the mark, the pH was checked, which should be 7.5. 0.1mL of the test serum was added to 6mL of zinc solution and nephelometric analysis was performed. The amount of class M Ig (macro globulins) was determined by optical density.

To determine class A Ig, a reagent was prepared, 1 liter of which contained 189.0g of ammonium sulfate and 29.3g of NaCl. This reagent can be stored for a long time in a closed container.

The determination process. 0.1mL of the test serum was added to 6mL of zinc solution and nephelometric analysis was performed. The amount of class A Ig was found from the obtained optical density and using a calibration graph. Reference immune sera of human and animal blood with a known concentration of Ig were used to plot the graph. For example: one ampoule (1mL) of the reference serum contains the following amounts of Ig of the corresponding class:

G: 11.94mg/mL or 1,194mg%

M: 1.33mg/mL or 133mg%

A: 1.88mg/mL or 188mg %

One standard ampoule of serum was taken, and 1mL of distilled water was added and dissolved without foaming. Then nine test tubes were taken, each previously filled with 1mL of saline solution. 1mL of the serum solution was transferred to the 1st tube, and thoroughly mixed, then 1mL of this solution was taken and transferred to the second tube. In the 9th tube, 2mL was obtained after mixing. Thus, the required amount of dilution of the standard solution with a predetermined amount of protein was achieved. The optical density of the solution was measured with a color density meter (CDM) at a wavelength of 400h using 10mL cuvettes. The test tubes with the same solutions, but without serum, were the control variant.

The determination of class G Ig was conducted in two test tubes. For the first test tube, a zinc-salicylic reagent of high ionic strength was prepared, which contained 1.875g of zinc sulfate and 57.14g of salicylic sodium. The pH value of such a solution should be 7.3. In the reaction of the first test tube, serum was used in which B-lipoproteins were removed since they are also precipitated by zinc-salicylic solution and increase the indicators. To remove them, 2mL, 0.025M of calcium chloride was poured into a test tube, and 0.2mL of the test serum and 0.04mL of 1% heparin solution were added to it. The mixture was stirred, while the solution became cloudy from the precipitation of B-lipoproteins. This mixture was placed in the refrigerator for 30 minutes to improve the flocculation reaction, then the precipitate was separated by centrifugation for 20 minutes at 4000rpm. The resulting supernatant was used for the reaction in an amount of 1.1mL. A quantity of 1.1mL of supernatant was added to 5mL of zinc-salicylic reagent, while class G Ig precipitated intensively. Nephelometric changes also occurred, and the amount of Ig was determined by the optical density.

The content of hemoglobin and red blood cells was determined by a photoelectric erythrohemometer using the method developed by Danilevskaya et al. (2005) and the number of white blood cells was calculated in the Goryaev chamber. The total protein levels in the blood serum were determined by the RL 140 refractometric method according to the refractive index of the substance, the levels of protein fractions were determined based on the turbidimetric nephelometric approach developed by (Kondrakhin et al. 2004).

Gas chromatography-mass spectrometry allowed us to identify disturbances of the intestinal microbiota in conditions of insufficient information capacity of routine bacteriological research and obtain an individual detailed microbiological passport.

Analysis and verification of results

The reliability of the data, main provisions, and scientific conclusions were substantiated by a large volume of preclinical and clinical studies using certified equipment, a wide range of methodological techniques, and statistical processing of digital material.

The effectiveness of the herbal remedy was assessed by the rate of disappearance of clinical signs of dyspepsia in calves and the results of hematological studies. All manipulations with animals were conducted in compliance with the rules of humane treatment.

RESULTS

None of the preparation components led to the death of experimental animals when it was administered orally. However, the reaction of mice to the introduced components was not the same and depended on the origin of the raw materials and preparation method. In animals receiving walnut infusion, reactions occurred immediately after administering the preparation under evaluation and manifested in the form of cramps. The mice first arched their backs and pressed their bellies to the floor of the cage. We noted an undulating movement of the trunk in the cranio-caudal direction, with paresis of the hind limbs. The mice were slowly moving into a corner, huddling together. Cessation of breathing lasting 3-5 seconds was noted. The clinical signs of intoxication lasted for 20-25 minutes. Then the writhing stopped, and the breathing became continuous but slow and shallow, but the movement of the animals around the cage was limited. We tend to associate the described respiratory disorders with superexcitation of *nervus vagus*.

During routine examination and assessment of the clinical condition of the mice in the following periods, no visible deviations were found between the groups. The

animals were active, did not differ from each other in behavioral reactions, and had a positive attitude toward food and water.

During the pathoanatomical autopsy of animals to study the possible consequences of the metatoxic effect of the preparation components, no pathological abnormalities between the groups in the internal organs were found.

Based on the reporting materials of the veterinary service of the Almaty and Turkestan regions, diseases of the digestive organs in the farms are constantly reported issues. In 2021-2023, the incidence of dyspepsia in the colostrum period in livestock farms, in calves born annually, ranged from 11 to 16%, and 18 to 24% of the sick animals died. In absolute numbers, the losses amounted to 6497 calves.

In the surveyed farms, the situation was approximately the same, with the usual elements of non-compliance with existing veterinary and sanitary standards. The cattle were kept in outdated standard cowsheds. The existing infrastructure for housing and raising newborn calves, including calving pens, prophylactic calf houses, and their primary equipment (such as cage boxes for newborn calves), was maintained in satisfactory condition. However, during the mass calving season in winter and spring, the water dispensed from nipple drinkers contained 103 *Escherichia coli* bacteria per milliliter. This translates to approximately 1,000 intestinal bacteria per liter of colostrum. Calving occurred in calving pens that were disinfected during the summer.

During mass calving, newborn calves stayed with their mothers for a significant part of the time before admission to the prophylactorium calf houses and received the first portion of colostrum in a cowshed. The average weight of newborns was 28-33kg; there was a significant percentage of the birth of underdeveloped calves (12-20%).

The results of the study of the quality of colostrum from mother cows that had calves with dyspepsia (Table 3) showed a connection between the unsatisfactory biochemical characteristics of colostrum in terms of acidity and total protein level with the incidence of dyspepsia in calves from the first days after birth, i.e., in the early neonatal period.

The calves were more likely to get sick on the first or second day after birth. The disease began with a 7.47-8.30% total protein content in the colostrum (while the norm is at least 14.92%) and its acidity equaling 27.6-29.4 T0. In hypotrophic calves, diarrhea was initiated by alimentary causes on the first day after birth, quickly acquiring a severe course.

The calves demonstrated loss of appetite, decrease in body temperature, diarrhea with copious liquid secretions with a large amount of mucus, exhaustion, tremors, staggering, depression, weak reaction to stimuli, depression of the eyeball, dryness of the nasal speculum, palpitations, shallow rapid respiratory movements, and cyanotic mucous membranes. Laboratory bacteriological studies and viral immunological analysis for the viral pathology of calves were negative.

Biochemical studies of blood sera from the mother stock of cows (Table 2) and colostrum performed to control the level of metabolism in maternal cows showed signs of chronic metabolic disorders in pregnant cows in dairy farms with frequent neonatal gastroenteritis in calves. There was a constant deficiency of total protein, calcium, phosphorus, and carotene in blood serum and colostrum.

The analysis of the totality of these data gives reason to believe that in the sum of the causes that result in the prevalence of dyspepsia in calves, a certain ecosystem conditionality dominates, caused by the problem of ensuring the full-fledged feeding of pregnant cows, which is the main component of the adequacy of the habitat for the breeding stock of cows and newborn cattle in dairy farms.

Thus, the etiology of dyspepsia in young cattle in the regional aspect is predominantly alimentary-deficient due to the imbalance of resources for biologically adequate feeding of the breeding stock of cows and newborn calves. This gives grounds to conclude that ecosystem factors determine the stationary state of gastrointestinal pathology in young cattle.

Based on our observations and the data of veterinary specialists, digestive pathology in various regions of Kazakhstan mainly affects calves under the age of 2 months. The peak of the disease occurs in the autumn/spring period. Animal treatment started after their isolation and diagnosis.

We found that the body temperature of calves with digestive disorders in both groups before treatment was higher than the physiological norm at an average level of 40.6±0.14°C in the CG and 40.4±0.36°C in the EG (Fig. 1). In clinically healthy calves, the body temperature was 39.2±0.11°C. The increase in body temperature is also evidenced by scientific data (Ramasubramaniaraja 2011; Lokireddy et al. 2013), which indicates an increase in this indicator in calf dyspepsia.

Heart rates in calves of both groups were equivalent, amounting to about 116.4±3.11 beats per minute in the CG and 112.6±2.48 in the EG, and were significantly higher than in healthy young calves (82.4±2.18) (Fig. 2). Studies on the effect of the methods of treatment of calves with dyspepsia used by us showed that the conducted therapeutic measures contributed to improving the overall clinical condition of calves. On the 4th day, the complete disappearance of the symptoms was not observed. The animals continued to be clinically monitored.

Table 3: Results (mean+SE) of biochemical analysis of colostrum of cows that had calves with dyspepsia

Indicator with a mild form of neonatal gastroenteritis	Units	Group of cows that had sick calves	
		With severe dyspepsia	With a mild form of dyspepsia
Turner acidity, T0	pH	27.6±1.3	29.4±1.2
Total proteins	%	8.30±0.4	7.47±0.4
Globulins	%	63.8±2.7	61.1±2.5
Calcium	g/L	0.185±0.3	0.183±0.3
Phosphorus	g/L	0.136±0.4	0.113±0.7
Carotene	mL%	0.07±0.001	0.03±0.001

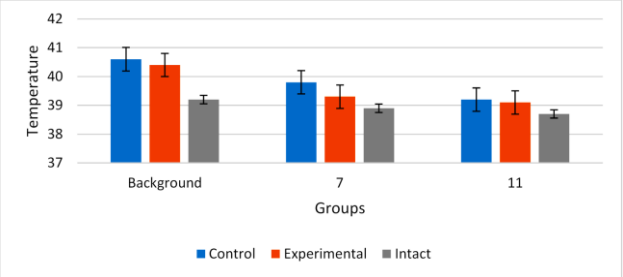

Fig. 1: The dynamics of body temperature.

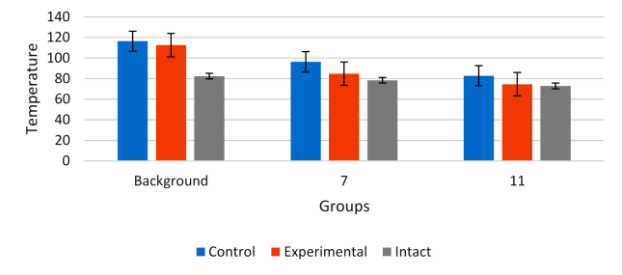

Fig. 2: The dynamics of heart rate.

Analysis of morphological blood composition showed that at the beginning of the experiment, the number of red blood cells in all sick calves was significantly lower than in the CG by 29.4% and in the EG by 28.2%. Erythropenia was accompanied by low hemoglobin concentrations in the CG and EG (12.7 and 14.4% lower than the norm, respectively) (P<0.05). Pronounced leukocytosis with a high level of the total number of white cells was noted, exceeding the same indicator of intact calves by 32.8% in the CG and 35.6 in the EG at P<0.05. Further analysis showed that using herbal remedies to treat young animals with digestive pathology led to changes in the indicators. On the 3rd day, the red blood cell content in the CG increased by 17.8% compared to the initial values, but their number remained slightly lower than in healthy livestock. In the EG, this indicator also increased and was close in quantitative terms to the values of the compared group. The hemoglobin level increased slightly in the blood of animals of both EGs, however; these values in the CG were lower than those of intact animals by 7.7%, without significant differences. In the EG, this indicator was close to the indicators of the reference group. Despite the disappearance of the main symptoms in the EG, the white blood cell counts and the red blood cell sedimentation rate indicated incomplete recovery, which was especially characteristic of the CG.

On the 5th day, all recorded indicators of the EG were close to the values of intact animals. In the CG, most animals also leveled with the reference group, but the number of red blood cells and hemoglobin concentration remained at a relatively low level compared to the intact group.

Unlike most indicators of morphological blood composition, the values of biochemical status were more informative. The blood serum values in all groups at the final stage of the experiment are presented in Table 4. The total protein content in the CG was significantly lower than in healthy calves by 11.6%. In the experiment, these indicators were also slightly lower than in the compared group, but the difference was insignificant.

Table 4: Mean+SE of Biochemical parameters of calf blood serum (n=5)

Indicator	Units	Groups		
		Intact	Control	Experimental
Total protein	g/L	67.2±1.18	59.4±1.12*	64.5±2.02
Albumins	g/L	42.4±1.22	34.2±0.88*	38.4±1.42
AST	IU/L	86.0±3.62	94.2±4.18	88.4±3.76
ALT	IU/L	34.6±1.28	42.5±1.22*	38.2±1.64
Alkaline phosphatase	IU/L	178.8±5.18	156.2±6.12	164.6±5.23

Provide explanation of * under the table.

Albumin content was higher in the blood serum in the EG, where its value exceeded the CG by 12.3%. However, this indicator was lower than in physiologically normal developed young animals by 9.4%. In the CG calves treated only with oxytetracycline, albumins were significantly lower than in the compared group by 19.3% at P<0.05.

We tend to associate a decrease in protein and albumin levels with metabolic restructuring and impaired liver function, which becomes a powerful organ in most pathologies of various etiologies. When analyzing the AST content in blood serum, an increased AST content was found in the CG, where its level exceeded the same indicator in healthy calves by 9.5%, but the difference was insignificant. In the calves of the EG and the intact group, this indicator was close in its values. In contrast, the ALT level was significantly higher than the same indicator in healthy young animals by 22.8% at P<0.05. In the EG, this indicator was slightly higher than in the intact group and amounted to 10.4%, but the difference was insignificant.

Another indicator of the number of enzymes we determined was alkaline phosphatase. Its content was 12.6% lower than in the compared group (P≥0.05). The EG calves also showed inferior results compared to the intact animals in this indicator but with no significant differences. Thus, the results of a biochemical study of blood serum in calves taking the phytopreparation and in animals without the support of the phytopreparation showed that throughout the experiment, a significant difference in blood parameters, such as alkaline phosphatase, ALT, and AST persisted, indicating a positive effect of the decoction.

To understand the effect of the walnut decoction on the state of immune protection in calves in the early postnatal period, an immunological study of animal blood serum was conducted, which included the study of the following indicators: IgA, IdM, and IgG. The results of the study of immunological blood parameters after two weeks of the experiment are presented in Table 5.

Table 5: Values (mean+SE) Immunoglobulins A, M and G (g/L) of calves' blood serum (n=5)

Indicator	Group	
	Control	Experimental
IgA	1.55±0.20	1.75±0.50
IgM	0.59±0.03	0.65±0.20
IgG	1.16±0.32	1.0±0.10

The indicators of IgA and IgM in both groups had no significant differences at 30 days of age (P>0.05) and amounted to 1.58±0.4 and 0.55±0.02g/L and 1.62±0.40 and 0.45±0.04g/L, respectively. The IgG values in the EG were significantly higher (P≤0.05) than in the CG and respectively amounted to 2.65±0.70 and 1.85±0.40g/L. Based on the obtained data, the phytopreparation has a

positive effect on the main immune parameters (IgA, IgM, IgG) of calves in the early postnatal period. A similar situation was observed concerning IgA, IgM, and IgG, the concentration of which in the blood of calves receiving the preparation at two weeks was 1.55±0.20, 0.59±0.03, and 1.16±0.32g/L, respectively. In the CG calves, it equaled 1.75±0.50, 0.65±0.20, and 1.0±0.10g/L. However, there were no significant differences in Ig values in these groups. Thus, including the walnut decoction in the treatment regimen increased the effectiveness of therapeutic measures by reducing the recovery time of calves with bronchopneumonia.

DISCUSSION

Digestive diseases occupy a leading place among other pathologies of young farm animals and cause significant economic damage to animal husbandry. Therefore, the search for effective methods and means of treatment remains an urgent task in modern veterinary medicine. At the Department of Clinical Veterinary Medicine of the KazNAIU, a phytopreparation was developed that includes plant components, a toxic and pharmacological assessment was given, and its therapeutic efficacy was studied when included in the treatment regimen of calves with dyspepsia.

Clinical studies showed that calves developed dyspepsia in the first days of life and had the same clinical symptoms. The calves showed general depression, became less active, and lay down more often. Their appetite was reduced at the beginning, and anorexia was recorded at the peak of the disease. The visible mucous membranes, as a rule, were anemic, and the body temperature was either at the upper limits of the normative values or subfebrile. In sick animals, the diarrheal syndrome was observed: increased intestinal peristalsis with intestinal auscultation, loud and constant rumbling, increased acts of defecation, shapeless feces with a pungent odor, and liquid consistency. The anal sphincter in severe dyspepsia was in a relaxed state; during rectal examination, liquid excrement with an admixture of mucus was observed in the rectum. The coat became dull and disheveled, and feces were found on the tail and pelvic limbs. The color of the feces was mostly yellow with varying intensities. The smell of the feces was pungent, sour, and putrid with a mixture of the smell of hydrogen sulfide. Mucus, gas bubbles, and undigested feed particles were often observed in the feces. Calves that did not take the herbal preparation significantly lagged behind the EG animals in body weight.

A comparative analysis of the two treatment regimens showed that in the EG calves, the duration of the disease was on average 2.5±0.3 days when treated with the phytopreparation. In animals that did not receive the preparation, signs of the disease persisted on average up to 5.2±0.5 days from the beginning of treatment according to the scheme adopted by the farm. Thus, the walnut decoction is a more effective remedy in the treatment of dyspepsia in calves in the early postnatal period. The results of an immunological study of blood serum after treatment showed that the level of IdM and IgG in animals treated with the phytopreparation was significantly higher than in animals treated according to the traditional scheme. The IgM and IgG levels in the EG were significantly higher ($P<0.05$) than in the CG (by 27.0 and 48.0%, respectively).

Based on vegetable raw materials, an infusion and decoction for parenteral use in calves with dyspepsia were developed for the first time. Based on the study, we developed and tested the phytopreparation to treat acute gastrointestinal pathology in young cattle. Therapeutic schemes of complex dyspepsia therapy in calves with the phytopreparation were developed (Turzhigitova et al. 2019).

For the first time, the analysis of the relationship between clinical variants of irritable bowel syndrome (with a predominance of obstruction and diarrhea) and clinical variants of functional dyspepsia (epigastric pain and postprandial distress syndrome) in their combined course was conducted. The approaches to improving the effectiveness of the traditional therapy of animals with combined functional digestive diseases when supplemented with release-active preparations were clarified (Busch et al. 2004; Boirivant and Strober 2007).

The implementation of phytopreparations in treating dyspepsia in calves follows current research trends and studies such as Zhylgeldieva et al. (2024), which aim to understand the effectiveness of herbal products as therapeutics in farm animals. There are insufficient studies to link the superexcitation of the vagus nerve to walnut phytopreparations, and this calls for more research on the biochemical composition of walnut phytopreparations and the effect on the nervous system. The low toxicity and safety of walnuts agree with recent studies on their pharmacological applications (Mozhaiev 2023). The connection between the characteristics of colostrum and dyspepsia aligns with Smolovskaya et al. (2022), who reiterated that the untimely intake of colostrum or intake of poor-quality colostrum violates the protective constitution of the body and can provoke gastrointestinal tract diseases. The symptoms, increased in temperature and heart rate, align with the report of Norboyev and Fayziyeva (2024) on their treatment of calf dyspepsia. Zhylgeldieva et al. (2024) confirm the effect of walnut phytopreparations. The improved synthesis of red and white blood cells after the intake of walnut phytopreparations agrees with the study of Zhou et al. (2022). The relatively low number of red blood cells and hemoglobin concentration in the treated calves when compared with the intact group highlights the presence of other crucial factors when treating dyspepsia. Norboyevich and Fakhriddinovna (2024) emphasize the need for proper diet and hygienic environmental conditions when dealing with calf dyspepsia. The reduction in AST and ALT levels after the application of the phytopreparation agrees with the *in vivo* studies of Miao et al. (2022). The effect of walnut phytopreparation on immunity agrees with Gasmi et al. (2023); although both studies focus on mammalian organisms, there is an insufficient number of studies on the effects of walnut phytopreparation on farm animal immunity, which creates a gap for future research. Fizeșan et al. (2021) highlight the antitussive, antioxidant, and anti-inflammatory effects of a walnut, which aligns with the results that walnut decoction reduces the recovery time of calves with bronchopneumonia. More research is recommended to understand the biochemical process behind this phenomenon. In comparison with the study carried out by Zhylgeldieva et al. (2024), we observe that clinical recovery was achieved at 7 days at 250mL of walnut

phytopreparations, which contrasts with the results obtained in this study where clinical recovery was reached at 5 days at 300mL of walnut phytopreparations. More research is recommended to understand the relationship between concentration, dosage form, and treatment speed and also possible toxic levels. Further research is recommended on the effect of walnut phytopreparation on cows during the gestation period and their possible effects on the calves (Mamenko et al. 2021).

Conclusion

Our main results are reflected in the following conclusions:

1. The technology of obtaining the phytopreparation (infusion and extract) from vegetable raw materials in liquid dosage form for parenteral use was developed. The product is a compound walnut preparation that includes tannins, alkaloids, flavonoids, terpene compounds, higher hydrocarbons, and 16 macro- and micronutrients.
2. The phytopreparation is low toxic for warm-blooded animals with oral and parenteral administration in doses of 20.0mL/kg of live weight. The median lethal dose (LD50) and the lethal dose (LD100) were not established. According to the classification of chemical compounds according to State Standard (GOST) 12.1.007-76, the preparation belongs to hazard class IV (low-toxic substances). The product did not demonstrate subchronic or chronic toxicity, local irritant, allergenic, embryotoxic, or teratogenic effects.
3. A three-time application of the phytopreparation in a dose of 250-300mL added to the main treatment of calves with dyspepsia reduced the recovery time by an average of 2.3 days.
4. In calves with dyspepsia, the phytopreparation reduced the normalization time of hematological and biochemical blood parameters. In the range of the terms of blood testing established for experiments, according to hemograms and protein metabolism, this was possible on the 5th day from the start of treatment.
5. In production conditions, the phytopreparation expands the practical therapeutic possibilities of combating dyspepsia in calves. This method in combination with conventional pathogenetic treatments can achieve therapeutic effectiveness of about 20-25% and reduce mortality by an average of 30%. Veterinary measures during the use of the phytopreparation in the experiment were 20% more effective than antibiotics.

New information was obtained on the modern concept of the mechanism of action of medicinal plants. The widespread use of preventive and curative measures outlined in this work allows to reduce the incidence of newborn calves with dyspepsia and ensure their safety in dairy farms, complexes, and farmsteads.

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