

Volodymyr Nadykto *Editor*

# Modern Development Paths of Agricultural Production

Trends and Innovations

 Springer

# Modern Development Paths of Agricultural Production

Volodymyr Nadykto  
Editor

# Modern Development Paths of Agricultural Production

Trends and Innovations

 Springer

*Editor*  
Volodymyr Nadykto  
Tavria State Agrotechnological University  
Melitopol, Ukraine

ISBN 978-3-030-14917-8                      ISBN 978-3-030-14918-5 (eBook)  
<https://doi.org/10.1007/978-3-030-14918-5>

Library of Congress Control Number: 2019935551

© Springer Nature Switzerland AG 2019

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publisher, the authors and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, expressed or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

This Springer imprint is published by the registered company Springer Nature Switzerland AG  
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

# Contents

## Part I

<b>Improving the Efficiency of Fruit Tree Sprayers</b> . . . . .	3
Nikolai Struchaiev, Larysa Bondarenko, Olexandr Vershkov and Andrei Chaplinskiy	
<b>Refractory Materials Manufacturing Based on Sewage Sludge</b> . . . . .	11
Ludmyla Chernyshova, Serhii Kiurchev, Oleg Peniov and Vitaliy Cherkun	
<b>Increasing the Efficiency of the Technological Process of Processing Castor-Oil Seeds into Castor Oil</b> . . . . .	17
Volodymyr Didur, Volodymyr Kyurchev, Andriy Chebanov and Anatoliy Aseev	
<b>Mechanism for the Maintenance of Investment in Agriculture</b> . . . . .	29
Halyna Hrytsaienko, Igor Hrytsaienko, Andriy Bondar and Dmitry Zhuravel	
<b>Location of Social Capital in the Labor Protection of the Enterprise</b> . . . . .	41
Mykola Hrytsaienko, Yuri Rogach and Mykhailo Zorya	
<b>Defining Stability of Technological Process of Growing Fruit Crop Seedlings</b> . . . . .	53
Oleksandr Karaiev, Lyudmyla Tolstolik, Ivan Chyzyhkov and Tetiana Karaieva	
<b>Design of Functional Surfaces in CAD System of SolidWorks via Specialized Software</b> . . . . .	63
Yuliia Kholodniak, Yevhen Havrylenko, Iryna Pykhtieieva and Viktor Shcherbyna	
<b>Seed Material Size Influence on Its Uniform Sowing Unit Delivery</b> . . . . .	75
Volodymyr Kiurchev, Yevhenii Serbii and Svitlana Shevchenko	

<b>Agrobiological as Well as Mechanical and Technological Framework of Development of the Harvesting Technology with the Method of Grain Crops Combing in Standing Position . . . . .</b>	<b>85</b>
Oleksandr Lezhenkin, Ivan Lezhenkin, Oleksandr Vershkov and Serhii Kolomiiets	
<b>Simulation of Cereal Crops Harvesting Using the Method of Grain Crops Combing in Standing Position in Conditions of Farming Enterprises . . . . .</b>	<b>91</b>
Oleksandr Lezhenkin, Ivan Lezhenkin, Oleksandr Vershkov and Serhii Kolomiiets	
<b>Software Development for the Security of TCP-Connections . . . . .</b>	<b>99</b>
Dmytro Lubko, Sergii Sharov and Oksana Strokan	
<b>The Formation of Orthogonal Balanced Experiment Designs Based on Special Block Matrix Operations on the Example of the Mathematical Modeling of the Pneumatic Gravity Seed Separator . . . . .</b>	<b>111</b>
Vira Malkina, Serhii Kiurchev, Viacheslav Osadchyi and Oksana Strokan	
<b>The Parameters Substantiation of Seed Drill Capacity for Stone Crop Seeds . . . . .</b>	<b>121</b>
Oleksandr Matkovskiy, Oleksandr Karaiev, Serhii Sankov and Tetiana Karaieva	
<b>Methodological Aspects of Determining Parameters of a Scalper-Type Air-Sieved Separator Airflow . . . . .</b>	<b>133</b>
Evgeniy Mikhailov, Marina Postnikova, Natalia Zadosnaia and Oleg Afanasyev	
<b>Theoretical Aspects of Plant Material Sealing in a Wedge-Shaped Canal . . . . .</b>	<b>139</b>
Dmytro Milko, Viacheslav Bratishko, Volodymyr Kuzmenko and Oleksandr Kholodiuk	
<b>Study of Hydromechanical Parameters Part of the Water Solutions Household in Running Flows . . . . .</b>	<b>145</b>
Serhii Movchan, Olena Dereza, Serhii Mazilin and Serhii Dereza	
<b>The Efficiency of Tractor Application with Articulated Frame for Cultivating Arable Crops . . . . .</b>	<b>161</b>
Volodymyr Nadykto, Oleksandr Karaiev, Volodymyr Kyurchev and Hristo Beloiev	
<b>Operating Conditions' Influence on the Change of Functional Characteristics for Mechatronic Systems with Orbital Hydraulic Motors . . . . .</b>	<b>169</b>
Anatolii Panchenko, Angela Voloshina, Irina Milaeva and Petro Luzan	

<b>Increase in Durability of Motor Crankshaft Pin Surface by Vibrorolling</b> .....	177
Oleksii Novyk, Valeriia Panina, Halyna Dashyvets and Andriy Bondar	
<b>The Coefficient Determination of a Damper Washer Hydraulic Resistance for Reducing a Technical Module Oscillation Amplitude</b> .....	183
Volodymyr Bulgakov, Oleksandr Parakhin, Vasil Mitkov and Tetiana Chorna	
<b>Generalization of Factors of Milk Homogenization</b> .....	191
Kyrylo Samoichuk, Nadiia Zahorko, Vadym Oleksiienko and Serhii Petrychenko	
<b>Setting Ground Dimension-Type Series-Tillage Fertilizing, Sowing Complexes for Growing Grain Crops</b> .....	199
Vitaliy Serbiy, Volodymyr Diuzhaiev, Halyna Antonova and Olena Mykhailenko	
<b>Consulting Services in Agriculture</b> .....	217
Nadiia Serskykh and Igor Britchenko	
<b>Development of Technology for the Hemp Stalks Preparation</b> .....	223
Viktor Sheichenko, Igor Marynchenko, Vitaliy Shevchuk and Natalia Zadosnaia	
<b>Theoretical Studies of Stable Exploitation Conditions of a Three-Wheeled Tractor on the Field Slopes</b> .....	233
Viktor Sheichenko, Gedal Hailis, Igor Dudnikov and Tetiana Chorna	
<b>Research of the Cereal Materials Micronizer for Fodder Components Preparation in Animal Husbandry</b> .....	249
Alexander Skliar, Boris Boltyanskyi, Natalia Boltyanska and Denis Demyanenko	
<b>Grains Dynamic Strength Determination and the Optimal Combination of Components of a Diamondiferous Layer of Grinding Wheels</b> .....	259
Olga Sushko, Serhii Kiurchev, Oleksandr Kolodii and Roman Bakardzhyiev	
<b>Application of Phenoclimatographic Models in Stone Fruits Protecting from Spring Frosts</b> .....	267
Valentyna Odyntsova, Serhii Sushko, Larysa Bondarenko and Nina Shcherbakova	
<b>Vacuum Cooling Technology for Pre-cooling of Cherry Fruits</b> .....	281
Oleksandr Lomeiko, Lilia Yefimenko and Vira Tarasenko	

<b>Sowing Units for Drilling Vegetable Crops</b> .....	289
Volodymyr Tarasenko, Larysa Bondarenko, Nina Shcherbakova and Natalia Horbova	
<b>Examining the Creative Potential of Engineering Students</b> .....	299
Natalia Sosnytska, Olena Titova, Svitlana Symonenko and Olena Kravets	
<b>Development of Communicative Competence as a Precondition of Competitive Software Engineer Formation</b> .....	307
Svitlana Symonenko, Nataliia Zaitseva, Olena Titova and Margaryta Vynogradova	
<b>Analysis of Main Process Characteristics of Infrared Drying in the Moving Layer of Grain Produce</b> .....	317
Igor Palamarchuk, Serhii Kiurchev, Liudmyla Kiurcheva and Valentyna Verkholantseva	
<b>Geometrical Parameters for Distribution Systems of Hydraulic Machines</b> .....	323
Angela Voloshina, Anatolii Panchenko, Igor Panchenko and Andrii Zasiadko	
<b>Part II</b>	
<b>Mathematical Model Changing the Value of the Process of Leakage Current in 0.38 kV Networks</b> .....	339
Viacheslav Gerasymenko, Volodymyr Kozyrskyi, Natalia Maiborodina and Oleksandr Kovalov	
<b>Experimental Study of Positive Influence on Growth of Seeds of Electric Field a High Voltage</b> .....	349
Vadim Hulevskyi, Yurii Stopin, Yulia Postol and Mariia Dudina	
<b>The Usage of Electricity Charged Aerosol for Greenhouse Cooling: Problems and Prospects</b> .....	355
Anton Kashkarov, Volodymyr Diordiiev, Andrii Sabo, Gennadii Novikov and Olexandr Diordiiev	
<b>Development of a Motor Speed Observer for a Electrified Soil-Cultivating Motoblock</b> .....	365
Oleksandr Kovalov, Sergey Kvitka, Oleksandr Solomakha and Viacheslav Gerasymenko	
<b>Experimental Investigations of Functional Properties of Biofuel Processed in the Electrotechnological Complex</b> .....	375
Kushlyk Ruslan, Nazarenko Igor and Kushlyk Roman	



<b>Hybrid Power System Stochastic Optimization</b> . . . . .	385
Olga Lysenko, Mykola Kuznetsov, Andriy Chebanov and Svitlana Adamova	
<b>Energy Saving in the Technological Process of the Grain Grinding</b> . . . . .	395
Marina Postnikova, Evgeniy Mikhailov, Dina Nesterchuk and Olga Rechina	
<b>Determination of the Duration of Spherical-Shaped Berries Freezing Under the Conditions Stationary Heat Flow</b> . . . . .	405
Nikolai Struchaiev, Yulia Postol, Yurii Stopin and Ivan Borokhov	
<b>Energy-Saving Control of Asynchronous Electric Motors for Driving Working Machines</b> . . . . .	415
Oleksandr Vovk, Sergey Kvitka, Serhii Halko and Oleksandr Strebkov	
<b>Part III</b>	
<b>The Role of Social Capital in Development of Agricultural Entrepreneurship</b> . . . . .	427
Mykola Hrytsaienko, Halyna Hrytsaienko, Larysa Andrieieva and Larysa Boltianska	
<b>Methodological Aspects of Forming Mathematic Models of Management of Socio-economic Systems Development</b> . . . . .	441
Oleksii Hudzynskiy, Yulia Hudzynska, Svitlana Sudomyr and Mariia Sudomyr	
<b>Modeling Innovative Economic Activity of Peasant Farm</b> . . . . .	451
Sergey Kalchenko, Tetiana Popova, Denis Eremenko and Larisa Eremenko	
<b>Prospects of Ukraine on the World Market of Dairy Desserts</b> . . . . .	463
Tatiana Krasnoded, Tetiana Popova, Tetiana Bakina and Olena Vasylychenko	
<b>Cognitive Modeling in the Regional Strategic Management</b> . . . . .	473
Olha Nazarova, Elena Shevchuk, Svitlana Plotnichenko and Nonna Surzhenko	
<b>Managing Competitiveness of the Enterprise: Theoretical-Methodological Aspect</b> . . . . .	483
Svitlana Nesterenko, Svitlana Rozumenko, Oleg Kravets and Liudmyla Redko	
<b>International Ranking and Clustering Systems in Complex Evaluation of Demographic and Migration Processes</b> . . . . .	493
Svitlana Nesterenko, Dmytro Vasylykivskiy, Raisa Kvasnytska and Ihor Lapshyn	

<b>Ukraine in the Context of the World Organic Production of Agricultural Products</b> .....	507
Roman Oleksenko, Iryna Kolokolchykova and Olena Syzonenko	
<b>Development and Incipience Decentralization of Authority in Ukraine and Formation of Its Impact on Local Budgets' Financial Capacity</b> .....	515
Svitlana Osypenko, Inna Kohut, Olena Iatsukh and Elvina Abliazova	
<b>Analyses of Personnel Usage at Agricultural Enterprises</b> .....	527
Yurii Prus, Tetiana Yavorska, Olena Voronianska and Olexiy Petryha	
<b>Methodical Approaches to Implementation of Financial Bank Stability</b> .....	547
Nataliia Radchenko, Natalia Rubtsova, Iryna Chkan and Inna Yakysheva	
<b>Accounting and Analytical Methods for Identifying Risks of Agricultural Enterprises' Sustainable Development</b> .....	561
Oleh Sokil, Zhuk Valeriy, Nataliia Holub and Olha Levchenko	
<b>Managing of the Living Quality of Population in the Social Sphere</b> .....	571
Lyudmyla Synyayeva, Nataliya Bocharova, Iryna Ahieieva and Anhelina Yarchuk	
<b>Accounting Essence of Amortization Policy</b> .....	583
Zhuk Valeriy, Trachova Dar'ya, Sakhno Ludmyla and Demchuk Olena	
<b>Problems and Prospects for Development of Family Households in Ukraine</b> .....	593
Tetiana Yavorska, Yurii Prus, Oksana Lysak and Hanna Zavadskykh	
<b>Part IV</b>	
<b>Comprehensive Assessment of the White Roots Aroma</b> .....	605
Iryna Bilenka, Yana Golinskaya, Iryna Kalugina and Liudmyla Kiurcheva	
<b>Influence of the Growth Regulator Application Method on Antioxidant Plant System Activity of Winter Wheat (<i>Triticum Aestivum</i> L.)</b> .....	615
Zoia Bilousova, Yuliia Klipakova, Victoria Keneva and Serhii Kulieshov	
<b>Effects of Different Dietary Selenium Sources Including Probiotics Mixture on Growth Performance, Feed Utilization and Serum Biochemical Profile of Quails</b> .....	623
Volodimir Bityutsky, Svitlana Tsekhmistrenko, Oksana Tsekhmistrenko, Olexander Melnychenko and Viktor Kharchyshyn	

<b>Influence of Oat Extract on the Antioxidant Status of Geese</b> . . . . .	633
Olena Danchenko, Lubov Zdorovtseva, Mykola Danchenko, Oleksandr Yakoviichuk, Tetiana Halko, Elena Sukharenko and Yulia Nicolaeva	
<b>Screening of Agricultural Raw Materials and Long-Term Storage Products to Identify Bacillary Contaminants</b> . . . . .	641
Olena Danylova, Marina Serdyuk, Liudmyla Pylypenko, Victor Pelykh, Inna Lopotan and Antonina Iegorova	
<b>Development of Formulation and Quality Assessment of Fast-Cooking Grain Composition for Pregnant Women</b> . . . . .	655
Nadya Dzyuba, Liubov Telezhenko, Maryana Kashkano and Oksana Maksymets	
<b>Innovative Technology of the Scoured Core of the Sunflower Seeds After Oil Expression for the Bread Quality Increasing</b> . . . . .	665
Victoria Evlash, Lydia Tovma, Iryna Tsykhanovska and Nonna Gaprindashvili	
<b>Effect of Living Mulch on Chlorophyll Index, Leaf Moisture Content and Leaf Area of Sweet Cherry (<i>Prunus avium</i> L.)</b> . . . . .	681
Tatyana Gerasko, Lyudmila Velcheva, Liudmyla Todorova, Lyubov Pokoptseva and Iryna Ivanova	
<b>Modification of Modeling Method of Toxic Dystrophy of Liver in Rats</b> . . . . .	689
Viktoriya Gryshchenko, Olena Danchenko and Viktoriya Musiychuk	
<b>Technological Properties of Winter Wheat Grain Depending on the Ecological and Geographical Origin of a Variety and Weather Conditions</b> . . . . .	699
Hrygoriy Hospodarenko, Olena Cherny, Ihor Prokopchuk and Marina Serdyuk	
<b>Multicriteria Optimization of Quality Indicators of Sweet Cherry Fruits of Ukrainian Selection During Freezing and Storage</b> . . . . .	707
Iryna Ivanova, Iryna Kryvonos, Liudmila Shleina, Galina Taranenko and Tatyana Gerasko	
<b>Effect of Preparations Methyure (6-Methyl-2-Mercapto-4- Hydroxypyrimidine) on Corn (<i>Zea Mays</i> L.) Biological Productivity Under Saline Soil Conditions</b> . . . . .	719
Maksym Kolesnikov, Yuliia Paschenko, Halyna Ninova, Maryna Kapinos and Anastasiia Kolesnikova	
<b>Sweet Ices with High Nutritional Value</b> . . . . .	729
Juliya Kozonova, Victoria Stepanova, Alla Salavelis and Alina Kulyk	

<b>Nitrogen in Soil Profile and Fruits in the Intensive Apple Cultivation Technology</b> .....	737
Tetiana Maliuk, Natalia Pcholkina, Liliia Kozlova and Oksana Yeremenko	
<b>Technological Indices of Spring Wheat Grain Depending on the Nitrogen Supply</b> .....	753
Larysa Novak, Vitalii Liubych, Serhii Poltoretskyi and Mykola Andrushchenko	
<b>Use of Alternative Types of Fuel for Grain Drying</b> .....	763
Nina Osokina, Hennadii Tkachenko, Yana Yevchuk and Olena Hryhorenko	
<b>Effect of Seed Sowing Period on Antioxidant Protection of Basil (<i>Ocimum basilicum</i> L.) Under Greenhouse Conditions</b> .....	769
Olesia Priss, Iryna Korotka, Galina Simakhina, Victoria Koliadenco and Tatiana Kolisnychenko	
<b>Determining the Risks of the Production Environment of an Agricultural Enterprise</b> .....	777
Yurii Rohach, Oleh Yatsukh and Mykhailo Zoria	
<b>Development of Emulsion Sauce Technology for Preventive Nutrition</b> .....	785
Liubov Telezhenko, Gennadiy Diduch, Svitlana Kolesnichenko and Valentina Zhukova	
<b>The Influence of AKM Growth Regulator on Photosynthetic Activity of Oilseed Flax Plants in the Conditions of Insufficient Humidification of the Southern Steppe of Ukraine</b> .....	793
Oksana Yeremenko, Svitlana Kalenska, Lyubov Pokoptseva and Liudmyla Todorova	
<b>Investigation of the Grinding Mode of the Enriched Wheat Products in the Rolling Mill 1-Grinding System of the Milling Mill of Wheat Grinding</b> .....	807
Olena Yermeeva, Yevgen Kharchenko, Hennadii Tkachenko, Iryna Shapoval and Olena Hryhorenko	

# Modification of Modeling Method of Toxic Dystrophy of Liver in Rats



Viktoriya Gryshchenko , Olena Danchenko  and Viktoriya Musiychuk 

## 1 Introduction

The liver is the largest digestive gland that plays an important role in providing homeostasis of the internal environment of the body and in the development of adaptive reactions, which is due to its participation in many metabolic processes, anatomical, and functional connections with other organs and systems of the body. Recently, the risk of developing hepatopathy is increasingly associated with irrational pharmacotherapy of the underlying disease [4, 23, 24]. Thus, the administration of tetracycline antibiotics (doxycycline, chlortetracycline, metacycline) causes the occurrence of mitochondrial cytopathies. Toxic hepatitis can occur both on the first day of taking an antibacterial drug and after a few months from the start of treatment. To determine the degree of damage to the liver parenchyma, it is recommended to study the activity of enzymes with various intracellular topographies [7, 11, 16, 19].

Clinical and morphological manifestations of toxic liver lesions are diverse [20]. There are three main types of damage: hepatocellular, cholestatic, and mixed. The target of toxic effects can be hepatocytes (dystrophy, necrosis), bile ducts and tubules (cholestasis), or sinusoidal cells (endothelium). Medication of the liver, in particular parenchyma damage in the form of functional disorders (induction of microsomal enzymes, hyperbilirubinemia), lead to necrosis or apoptosis. Other hepatotoxic effects of pharmacotherapy include the formation of steatosis in the form of acute fat changes, steatohepatitis, cholestasis, granulomatous changes and damage to the vascular system of the liver, etc. [3, 5, 17].

---

V. Gryshchenko (✉) · V. Musiychuk  
National University of Life and Environmental Sciences of Ukraine,  
Heroiv Oborony Str., 15, Kiev 03041, Ukraine  
e-mail: [viktoriya\\_004@ukr.net](mailto:viktoriya_004@ukr.net)

O. Danchenko  
Tavria State Agrotechnological University, B. Khmelnytsky Av., 18,  
Melitopol, Zaporizhia Region 72312, Ukraine

A significant compensatory antitoxic reserve of the body neutralizes the negative impact of toxic substances [9, 18]. In the liver, which performs a detoxification function, their inactivation and binding take place for further elimination. The realization of this function during the first phase depends significantly on the activity of cytochrome P450. With the participation of the corresponding enzymatic systems, oxidation, reduction, hydrolysis, hydration, and dehalogenation of toxins occur [10]. In the next phase is registered conjugation of toxic substances and their deactivation due to the processes glucuronidation, acetylation, methylation, binding with amino acids and glutathione. However, the detoxification capacity of the organ is significantly reduced if the influence of harmful factors develops against the background of hepatopathology. The severity and severity of symptoms are determined by the dose of xenobiotics [2].

Morphological heterogeneity of toxic lesions of the liver and preferential localization of necrosis causes metabolic zoning. Behind metabolic activity, hepatocytes are heterogeneous. Their zoning for a difference in metabolic functions determines the selective sensitivity of hepatocytes to various pathological factors. In particular, cells of zone I contain more mitochondria, oxidative processes, gluconeogenesis, synthesis of cholesterol, urea, and bile acids are more intensive. In hepatocytes of the III zone, glycolysis, lithogenesis, cytochrome P450-dependent hydroxylation, and glucuronidation of xenobiotics are most pronounced. The use of tetracycline antibiotics leads to the development of necrosis of hepatocytes predominantly of the III zone [4].

Toxic liver damage due to taking medications presents a certain diagnostic complexity [1, 15]. Sometimes, with prolonged therapy, they proceed without clinical manifestations, which indicate chronic intoxication. This leads to a comprehensive study of the pathogenesis of the development of drug hepatopathology, primarily at the molecular level, the creation of sensitive test systems for early diagnosis, as well as the means of prevention and therapy of such conditions [6]. Therefore, it remains relevant to develop methods for the artificial reproduction of pathological conditions of the liver due to its medicinal damage. We have already developed a method for modeling drug-induced hepatopathy by introducing into the body of rats a non-steroidal anti-inflammatory drug diclofenac sodium, which provokes the development of toxic hepatitis [12].

The purpose of this work was the artificial reproduction in laboratory rats of an acute form of toxic hepatodystrophy without sudden changes in the clinical state, which corresponds to the spontaneous course of this hepatopathology in animals with respect to the complex of general clinical, biochemical, morphological, and pathoanatomical changes, but does not lead to death.

## 2 Experimental Studies

### 2.1 *Research Method and Materials*

**The Modeling of Toxic Hepatodystrophy.** The experiment involved white laboratory rats (males) who were selected according to the principle of analogues with a body weight of 200–220 g. With the known scheme for modeling fatty hepatosis in laboratory rats by oral administration of 1% solution of tetracycline hydrochloride at a dose of 500 mg/kg, for 5 days, an extremely severe clinical condition is observed, which develops already on the 2–3th day of the experiment, a lethal outcome is possible [13]. In addition, this type of animal with a body weight of 200–220 g is difficult to perceive the recommended volume of tetracycline hydrochloride solution, which borders or even exceeds the physiological capabilities of the stomach, and this in most cases is 5 cm<sup>3</sup> or more. This was the basis for work on improving the existing method for modeling the acute form of toxic hepatodystrophy. For this, two groups (control and study) were formed in twenty rats each. The animals of the study group artificially reproduced the acute form of hepatodystrophy by the method [9] of intragastric injection of the 4% solution of tetracycline hydrochloride, modified by us, using a probe at a dose of 250 mg/kg once a day, for 7 days in accordance with the current standardization and quality criteria conducting biological experiments and biomodeling principles [21]. Animals of the study group remained during the experiment without treatment. In the control group, clinically healthy rats were treated, with an equivalent volume of distilled water administered intragastrically by means of a probe.

The rats were separately placed in cages. Before the experiment began, they were in quarantine with a clinical examination for two weeks. The animals were kept on a balanced diet containing all the necessary biologically active and nutritious substances. They had free access to feed and drinking water. Were monitored changes in body weight and animal feed intake. The duration of the experiment was 7 days. Euthanization of animals and selection of biological material were carried out on the 8th day of the experiment.

During the experiment followed the requirements of the “European Convention for the Protection of Vertebrates used for experimental and scientific purposes” (Strasbourg, 1986), the Law of Ukraine “On the Protection of Animals against Cruel Treatment” No. 3447 of 21.02.2006.

**Histomorphological Studies.** After decapitation, a pathological anatomical dissection and selection of liver samples were performed for histomorphological studies. Pieces of liver were selected for microscopic studies and were fixed in a 10% solution of neutral buffered formalin [14], washed in running water, dehydrated in spirits of increasing concentration (70°, 96°), aged in chloroform, and poured into paraffin. The cooled paraffin blocks were attached to wooden cubes. After that, slices were made on a sine microtome, and slices 10 μm thick were obtained. The resulting sections were glued onto slides, stained with hematoxylin Karatsu and eosin, and examined with a light microscope [21].

**Morphological and Biochemical Studies of Blood.** Native blood was collected from rats from the abdominal aorta into test tubes with heparin solution, which was examined for hemoglobin content, absolute number of erythrocytes, leukocytes, and platelets, calculated by leukogram, and thrombocrit was determined on a Micro CC-20 Plus Auto HTI (USA) analyzer. To obtain plasma, it was centrifuged at 1500 rpm for 15–20 min. In blood plasma of rats were investigated biochemical indicators, such as total protein, total and conjugated bilirubin, activity of aspartate-aminotransferase (AST, EC 2.6.1.1), alanine-aminotransferase (ALT EC 2.6.1.2),  $\gamma$ -glutamyl-transpeptidase ( $\gamma$ -GTP, EC 2.3.2.2), alkaline phosphatase (APF, EC 3.1.3.1) on an open biochemical semi-automatic analyzer GBG Stat Fax 1904 Plus (Awareness Technology, Inc., Florida, USA) using DAC-SPECTROMED SRL (Moldova) reagents.

**Statistics.** The results were processed in the package Statistica 6.0. The probability of the difference between the samples was estimated by Student's *t* test, having previously checked the normality of their distribution. The disagreements were considered reliable at  $P < 0.05$ .

## 2.2 Results and Discussion

Regular administration of tetracycline hydrochloride preparation to rats for seven days is accompanied by the emergence of severe clinical symptoms of acute toxic dystrophy of liver that begin to appear in animals on the second or third day of its administration and are characterized by general depression, decreased appetite, polydipsia or thirst reduction, losses the average body weight for the group of 10–15 g, a dull coat, a decrease in elasticity and dry skin, hair loss, a slight increase stomach, liquefaction of stool.

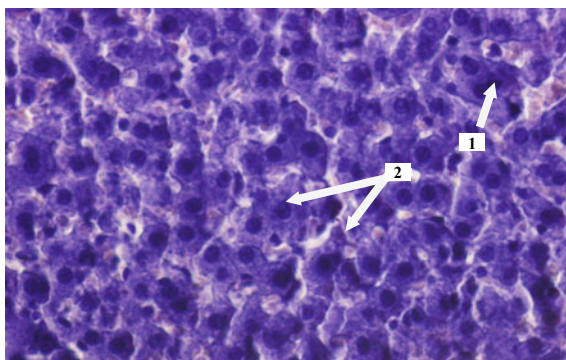
**Pathoanatomical Studies.** Data from the clinical manifestation of toxic hepatodystrophy complement the results of pathoanatomical studies of the body—the liver acquires a light yellow color or has a mottled mosaic pattern, the brownish-red areas alternate with yellow, slightly enlarged, rounded edges, flabby consistency.

**Histomorphological Studies.** Histomorphological examination shows the decomposition of hepatocytes, diffuse placement of fat droplets of different sizes (small, medium, and large droplets) in liver cells, focal histiolymploid infiltration, expansion, and blood vessel overflow (Fig. 1). In addition to obesity, a pronounced granular dystrophy is revealed. In some places, there are small proliferates of Kupffer cells. Changes in portal tracts are expressed in sclerosis with a slight thickening and inflammatory response—the appearance of small, local histiocytic, and lymphoid elements [22].

**Morphological Indicators of Blood.** As a result of the study of the morphological composition of the blood (Table 1), the development of leukocytosis (27% increase in the number of white blood cells), erythrocytopenia (a decrease in the number of erythrocytes by 27%), and simultaneous manifestation of hypochromaemia (a decrease in hemoglobin by 23%) was established in rats of the experimental group.



**Fig. 1** Liver of the rat of study group (a dose of tetracycline hydrochloride 250  $\mu\text{g}/\text{kg}$ ). Hepatocytes in the state of fatty degeneration (1), hyperemia of the vessels of the particle (2). Stained with hematoxylin Karatsu and eosin,  $\times 200$



**Table 1** Morphological blood indices of experimental hepatodystrophy rats against tetracycline hydrochloride at a dose of 250 mg/kg ( $M \pm m$ ,  $n = 20$ ,  $P < 0.05$ )

Index	Control group	Study group
Leukocytes, $10^9/\text{l}$	$4.8 \pm 0.2$	$6.1 \pm 0.5^*$
Erythrocytes, $10^{12}/\text{l}$	$6.6 \pm 0.5$	$4.8 \pm 0.3^*$
Hemoglobin (g/l)	$182.7 \pm 12.1$	$141.0 \pm 3.6^*$
Mean hemoglobin in erythrocyte	$28.3 \pm 1.1$	$29.5 \pm 1.7$
Hematocrit (%)	$35.2 \pm 2.3$	$27.2 \pm 1.7^*$
Platelets, $10^9/\text{l}$	$470.0 \pm 18.0$	$515.0 \pm 21.0$
Thrombocrit (%)	$0.249 \pm 0.018$	$0.322 \pm 0.016^*$
Lymphocytes (%)	$54.0 \pm 1.1$	$52.0 \pm 1.1$
Stab neutrophils (%)	$8.0 \pm 0.2$	$5.5 \pm 0.5^*$
Segmented neutrophils (%)	$33.5 \pm 0.8$	$36.0 \pm 0.4^*$
Monocytes (%)	$2.5 \pm 0.1$	$2.5 \pm 0.1$
Eosinophils (%)	$1.5 \pm 0.2$	$3.5 \pm 0.5^*$
Basophils (%)	$0.5 \pm 0.0$	$0.5 \pm 0.1$

\* results were significant for  $p \leq 0.05$  when compared to control meanings

At the same time, the average hemoglobin content in the erythrocyte remains unchanged; it may be a compensatory response to the development of anemia, which we also observed when rats were administered toxic doses of diclofenac sodium [8]. Simultaneous reduction of the hematocrit value by 1.3 times is probably a consequence of a significant decrease in the number of erythrocytes ( $P < 0.05$ ) and consequently proves the presence of anemia in patients with rats. The reason for increasing the value of thrombocrit (by 1.3 times), first of all, may be a violation in the hematopoiesis system or the result of the body's reaction to the development of other pathological processes that lead to stimulation of platelet production and change the parameters of the state of the platelet unit. We have diagnosed changes in

**Table 2** Biochemical indicators of blood plasma in rats of experimental tetracycline-induced hepatitis ( $M \pm m$ ,  $n = 20$ ,  $P < 0.05$ )

Index	Control group	Study group
Total protein (g/l)	68.0 ± 0.1	60.5 ± 0.1*
Total bilirubin (μmol/l)	3.2 ± 0.1	45.6 ± 2.9*
Conjugated bilirubin (μmol/l)	1.45 ± 0.23	27.33 ± 0.81*
Alanine aminotransferase (U/l)	24.12 ± 3.31	72.05 ± 2.38*
Aspartate aminotransferase (U/l)	71.25 ± 3.11	126.83 ± 4.04*
Alkaline phosphatase (U/l)	250.02 ± 10.02	400.10 ± 9.79*
γ-Glutamyl transpeptidase (U/l)	12.32 ± 0.68	21.34 ± 1.10*

\* results were significant for  $p \leq 0.05$  when compared to control meanings

thrombocrit in the body of animals suffering from toxic hepatodystrophy, probably due to the development of an acute inflammatory reaction in the liver parenchyma, which is confirmed by the presence of leukocytosis in these animals. In the leukogram of sick animals, a significant increase in the relative number of segmented neutrophils in 1.1 times is observed, along with a decrease in the number of stab nuclear (1.5 times), which indicates a shift of the nucleus of neutrophils to the right and, above all, is the result of toxic effects of tetracycline hydrochloride on the bone marrow.

For these animals, an increase in the amount of eosinophils in the blood is 2.3 times, which is explained by their known antitoxic function. They adsorb toxic products of protein nature and destroy them, and in areas of inflammation phagocytic immune complexes, products of tissue decay, although their phagocytic activity is lower than neutrophils.

**Biochemical Indicators of Blood.** In the study of biochemical indicators of blood plasma in patients with toxic hepatodystrophy in rats (Table 2), there is a significant increase in activity of liver-specific enzymes: alanine aminotransferase 3 times, aspartate aminotransferase—81%, alkaline phosphatase—60% and γ-glutamyl transpeptidase 73% with a simultaneous decrease in the total protein content by 11%, an increase in the concentration of total bilirubin by 15 times due to the conjugated fraction, the level of which increased by 19 times compared to the control, indicating destruction changes in hepatocytes, a decrease in the intensity of protein-synthesizing processes, a violation of pigment metabolism, and the development of intrahepatic cholestasis.

Thus, we proposed a method for modeling the acute form of toxic drug-induced hepatodystrophy in laboratory rats with pronounced clinical, pathologic-anatomical, and biochemical changes in both the liver and the level of the whole organism.

This experimental model can be used, first of all, in medicine and veterinary medicine in order to determine the peculiarities of ultrastructural and metabolic changes in the animal organism in the development of toxic liver dystrophy, as well as for the clinical testing of hepatoprotective profile preparations again and introduction of effective treatment regimens in animal husbandry with a similar manifestation spontaneous hepatopathology. The most important result of the development of experimental hepatodystrophy is the obtaining of desired changes in the liver parenchyma with relatively moderate clinical course in rats and their 100% survival rate.

### **3 Conclusions**

#### ***3.1 Tetracycline-Induced Hepatosis***

As a result of intragastric administration of 4% tetracycline hydrochloride solution to laboratory rats using a probe at a dose of 250 mg/kg once a day, for 7 days a complex of symptoms characteristic for acute toxic dystrophy of liver with an average severity of clinical course and absence lethal cases were marked. Regular administration of tetracycline hydrochloride preparation to rats for seven days is accompanied by the emergence of severe clinical symptoms of acute toxic dystrophy of liver that begin to appear in animals on the second or third day of its administration and are characterized by general depression, decreased appetite, polydipsia or thirst reduction, losses the average body weight for the group of 10–15 g, a dull coat, a decrease in elasticity and dry skin, hair loss, a slight increase stomach, liquefaction of stool.

#### ***3.2 Pathological Changes in the Liver***

In experimental hepatodystrophy—the liver acquires a light yellow color or has a mottled mosaic pattern, brownish-red areas alternate with yellow, slightly enlarged, rounded edges, flabby consistency. Histomorphological examination shows decomposition of hepatocytes, diffuse placement of fat droplets of different sizes in liver cells, focal histophilic infiltration, expansion, and overflow with blood vessels. In addition to obesity, a pronounced granular dystrophy is revealed.

#### ***3.3 Morphological Indicators of Blood***

For patients with toxic hepatodystrophy in rats, the development of leukocytosis, erythrocytopenia with simultaneous manifestation of hypochromia, a decrease

in the hematocrit size and growth of thrombocrit is characteristic, which indicates that these animals have an inflammatory process and anemia. In the leukogram of sick animals, there is a shift of the nucleus of neutrophils to the right, which, above all, is the result of toxic effects of tetracycline hydrochloride on the bone marrow. For these animals is characteristic eosinophilia, which is explained by their antitoxic function of eosinophils.

### 3.4 Biochemical Indicators of Blood

For the biochemical profile of the blood plasma of patients with toxic hepatodystrophy in rats, an increase in activity of enzymes relatively specific for the liver is characteristic: aminotransferases, alkaline phosphatase and  $\gamma$ -glutamyl transpeptidase and hypoproteinemia, hyperbilirubinemia due to the conjugated fraction, which indicates destructive changes in hepatocytes, a decrease in the intensity of protein-synthesizing processes, violation pigment metabolism, and development of intrahepatic cholestasis.

**Finding.** A method for modeling the acute form of toxic medicamentous hepatodystrophy has been developed. It can be used in experimental medicine and veterinary medicine to determine the peculiarities of ultrastructural and metabolic changes in the organism of animals with a similar spontaneous pathology of the liver, as well as for the clinical testing of hepatoprotective profile preparations again.

## References

1. Calitz, C., Hamman, J.H., Fey, S.J., Wrzesinski, K., Gouws, C.: Recent advances in three-dimensional cell culturing to assess liver function and dysfunction: from a drug biotransformation and toxicity perspective. *Toxicol. Mech. Methods* **28**(5), 369–385 (2018). <https://doi.org/10.1080/15376516.2017.1422580>
2. Chernova, V.M.: Liver pathology in patients with blood diseases. *Mod. Gastroenterol.* **3**(89), 105–113 (2016) (in Ukrainian)
3. Choi, Y.J., Lee, C.H., Lee, K.Y., Jung, S.H., Lee, B.H.: Increased hepatic fatty acid uptake and esterification contribute to tetracycline-induced steatosis in mice. *Toxicol. Sci.* **145**(2), 273–282 (2015). <https://doi.org/10.1093/toxsci/kfv049>
4. Deng, Z., Yan, S., Hu, H., Duan, Z., Yin, L., Liao, S., Sun, Y., Yin, D., Li, G.: Proteomic profile of carbonylated proteins in rat liver: discovering possible mechanisms for tetracycline-induced steatosis. *Proteomics* **15**(1), 148–159 (2015). <https://doi.org/10.1002/pmic.201400115>
5. Fabbrini, E., Magkos, F.: Hepatic steatosis as a marker of metabolic dysfunction. *Nutrients* **7**(6), 4995–5019 (2015). <https://doi.org/10.3390/nu7064995>
6. Forsberg, K.J., Patel, S., Wenczewicz, T.A., Dantas, G.: The tetracycline destructases: a novel family of tetracycline-inactivating enzymes. *Chem. Biol.* **22**(7), 888–897 (2015). <https://doi.org/10.1016/j.chembiol.2015.05.017>
7. Gryshchenko, V.A.: Biochemical properties of the plasma of rats with the experimentally induced hepatitis after oral administration of sodium diclofenac. *Regul. Mech. Biosyst.* **8**(2), 191–196 (2017). <https://doi.org/10.15421/021730> (in Ukrainian)

8. Gryshchenko, V.A.: Hematological profile of rats in experimental diclofenac-induced hepatitis. *Ukrainian J. Ecol.* **7**(3), 78–83 (2017). <https://doi.org/10.15421/2017073> (in Ukrainian)
9. Gryshchenko, V.A., Tomchuk, V.A., Musiychuk, V.V.: Method modeling of fatty liver. Patent UA, 105657 (2016) (in Ukrainian)
10. Madian, A.G.: Redox proteomic investigation of tetracycline-induced steatosis. *Proteomics* **15**(1), 8–9 (2015). <https://doi.org/10.1002/pmic.201400554>
11. Markley, J.L., Wencewicz, T.A.: Tetracycline-inactivating enzymes. *Front. Microbiol.* **9**(1058) (2018). <https://doi.org/10.3389/fmicb.2018.01058>
12. Melnychuk, D.O., Gryshchenko, V.A.: Method modeling of toxic hepatitis. Patent UA, 105657 (2016) (in Ukrainian)
13. Melnychuk, D.O., Tomchuk, V.A., Yanchuk, P.I., Gryshchenko, V.A., Reshetnyk, E.M., Synelnyk, T.B., Capenko, P.K., Kartyfuzova, ZhV, Govorukha, T.M., Makarchuk, MYu., Veselskyj, S.P.: Research Methods of Liver and Biliar System Functional State. NUBiP Ukraine, Kyiv (2015) (In Ukrainian)
14. Pototsky, M.K.: Fundamentals of Histopathological Engineering: Methodical Instructions. NUBiP Ukraine, Kyiv (2001) (In Ukrainian)
15. Schueller, F., Roy, S., Vucur, M., Trautwein, C., Luedde, T., Roderburg, C.: The role of miRNAs in the pathophysiology of liver diseases and toxicity. *Int. J. Mol. Sci.* **19**(1), 261 (2018). <https://doi.org/10.3390/ijms19010261>
16. Schwartz, J., Holmuhamedov, E., Zhang, X., Lovelace, G.L., Smith, C.D., Lemasters, J.J.: Minocycline and doxycycline, but not other tetracycline-derived compounds, protect liver cells from chemical hypoxia and ischemia/reperfusion injury by inhibition of the mitochondrial calcium uniporter. *Toxicol. Appl. Pharmacol.* **273**(1), 172–179 (2013). <https://doi.org/10.1016/j.taap.2013.08.027>
17. Szalowska, E., van der Burg, B., Man, H.Y., Hendriksen, P.J.M., Peijnenburg, A.A.C.M.: Model steatogenic compounds (amiodarone, valproic acid, and tetracycline) alter lipid metabolism by different mechanisms in mouse liver slices. *PLoS ONE* **9**(1), e86795 (2015). <https://doi.org/10.1371/journal.pone.0086795>
18. Thakkar, S., Chen, M.J., Fang, H., Liu, Z.C., Roberts, R., Tong, W.D.: The liver toxicity knowledge base (LKTb) and drug-induced liver injury (DILI) classification for assessment of human liver injury. *Expert Rev. Gastroenterol. Hep.* **12**(1), 31–38 (2018). <https://doi.org/10.1080/17474124.2018.1383154>
19. Tikhonov, S.N., Rotov, K.A., Alekseev, V.V., Snatnikov, E.A., Khrapova, N.P.: Activity of some enzymes in the liver of experimental animals after treatment with the liposomal formulation of tetracycline and streptomycin. *Bull. Exp. Biol. Med.* **149**(1), 47–49 (2010). <https://doi.org/10.1007/s10517-010-0872-9>
20. Tikhonov, S.N., Rotov, K.A., Khrapova, N.P., Alekseev, V.V., Snatnikov, E.A., Zamarin, A.A., Simakova, N.A.: Effect of liposomal tetracycline hydrochloride on enzymatic function of the liver. *Bull. Exp. Biol. Med.* **145**(4), 443–445 (2008). <https://doi.org/10.1007/s10517-008-0113-7>
21. Vlizlo, V.V., Fedoruk, R.S., Ratysh, I.B.: Laboratory Methods of Investigation in Biology, Stock-Breeding and Veterinary. Spolom, Lviv (2012) (in Ukrainian)
22. Volkova, O.V., Eletsy, Yu.K.: Fundamentals of Histology and Histological Techniques. Medicine, Moscow (1987) (In Russian)
23. Yao, X.M., Li, Y., Li, H.W., Cheng, X.Y., Lin, A.B., Qu, J.G.: Bicyclol attenuates tetracycline-induced fatty liver associated with inhibition of hepatic ER stress and apoptosis in mice. *Can. J. Physiol. Pharmacol.* **94**(1), 1–8 (2016). <https://doi.org/10.1139/cjpp-2015-0074>
24. Yu, H.-Y., Wang, B.-L., Zhao, J., Yao, X.-M., Li, Y.: Protective effect of bicyclol on tetracycline induced fatty liver in mice. *Toxicology* **273**(1–3), 60–60 (2010). <https://doi.org/10.1016/j.tox.2010.03.010>