

DOI: <https://doi.org/10.31640/LS-2025-4-18>

UDC 615.322:612.015.3:616.36-002:599.323.4



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THE EFFECT OF NATIVE AND MODIFIED LINGONBERRY LEAF EXTRACTS (*Vaccinium vitis-idaea* L.) ON THE STATE OF FREE RADICAL OXIDATION PROCESSES UNDER CONDITIONS OF PARACETAMOL-INDUCED HEPATITIS IN RATS

Abstract. One of the most frequently used over-the-counter drugs in the world is paracetamol (N-acetyl-para-aminophenol or acetaminophen). This drug is widely used for the symptomatic treatment of headache, muscle, joint, dental, and menstrual pain, as well as an antipyretic agent for acute respiratory infections, etc. However, prolonged use of paracetamol or its use in high doses can lead to the development of hepatitis and acute liver failure. For the prevention and therapy of such liver injuries, acetylcysteine is often used, in addition to hepatoprotectors, including those of plant origin. The aim of the study was to investigate the effect of native and L-arginine-modified thick extracts of cowberry leaves on the state of the antioxidant system under conditions of acute paracetamol-induced hepatitis in rats. It was established that the application of native thick and L-arginine-modified cowberry leaf extracts significantly ($p \leq 0.05$) reduces the level of 8-isoprostane, increases the pool of reduced glutathione, decreases the level of oxidized glutathione, and also increases catalase activities. Regarding the effect on reducing the level of 8-isoprostane, the L-arginine-modified cowberry leaf extract significantly outperformed the effect of the comparison drugs, Silibor and Argiclin. Regarding the effect on the parameters of the glutathione system and catalase, the efficacy of the L-arginine-modified cowberry leaf extract significantly ($p \leq 0.05$) exceeded the effect of the comparison drugs, Silibor and Argiclin. Evidently, the hepatoprotective properties of the extracts are due to the complex effect of the sum of catechins, hydroquinone derivatives, hydroxycinnamic acids, and flavonoids, which possess antioxidant and cytoprotective properties. The obtained data indicate the prospects for further in-depth studies of the hepatoprotective action of the L-arginine-modified thick extract of cowberry leaves.

Keywords: paracetamol-induced hepatitis; lingonberry leaf extract; lipid peroxidation; hepatoprotective activity; antioxidant activity; rats; L-arginine.

INTRODUCTION

One of the most frequently used over-the-counter drugs worldwide is paracetamol (N-acetyl-para-aminophenol or acetaminophen). This drug is widely used for the symptomatic treatment of

headache, muscle, joint, dental, and menstrual pain, as well as an antipyretic agent for acute respiratory infections, etc. [1].

According to modern views on the mechanism of action of paracetamol, it is currently believed to selectively inhibit cyclooxygenase (COX, likely COX-3) and, consequently, suppress the synthesis of prostaglandin PGE₂ predominantly in the central nervous system (CNS) rather than in peripheral tissues. The drug practically lacks an anti-inflammatory effect because cellular peroxidases under inflammatory conditions prevent the interaction of paracetamol with the active center of COX, which precludes its anti-inflammatory action.

In recent years, numerous publications in foreign editions have addressed other mechanisms of paracetamol action, including influence through the endocannabinoid system. As known, paracetamol is metabolized and deacetylated to p-aminophenol in the liver [1, 2]. This metabolite crosses the blood-brain barrier and is metabolized to N-arachidonoylphenolamine (AM404), which activates the endocannabinoid system, providing the drug's significant analgesic effect [3]. The interaction of paracetamol metabolites with the Transient Receptor Potential Vanilloid-1 (TRPV1) receptor, which is also involved in pain modulation, is also considered [4]. Despite the proven analgesic and antipyretic effect, good safety profile, and low cost demonstrated in many studies, the narrow therapeutic window and over-the-counter status of paracetamol lead to this drug remaining the leading cause of both acute liver failure (ALF) and other drug-induced liver injuries [5].

According to the American monitoring system for liver injuries– the Acute Liver Failure Study Group (ALFSG) –almost 46% of all cases of ALF in the USA are caused by paracetamol. Paracetamol overdose causes about 56,000 emergency department visits annually, 26,000 hospitalizations, and approximately 500 fatalities per year [5, 6].

According to the European Association for the Study of the Liver (EASL), paracetamol remains the leader among causes of direct (dose-dependent) hepatotoxicity [7, 8].

Several theories of paracetamol hepatotoxicity are currently considered [9, 10]. The most common is the theory of metabolic transformations. Paracetamol is largely metabolized in the liver through glucuronic acid conjugation and sulfuric acid conjugation. Approximately 4% of paracetamol in the liver is converted into the metabolite N-acetyl-p-benzoquinone imine (NAPQI) with the participation of cytochromes P450, particularly CYP2E1, CYP1A2, and CYP3A4. Under conditions of glutathione (GSH) depletion, NAPQI covalently binds to cysteine groups of proteins, forming adducts [11], including those in mitochondria [12].

The binding of NAPQI to mitochondrial proteins inhibits the mitochondrial respiratory chain, uncouples tissue respiration and oxidative phosphorylation, and promotes the excessive generation of reactive oxygen species (ROS). This leads to the activation of c-Jun N-terminal kinase (JNK) [11]. Phosphorylated JNK translocates to the mitochondria, which enhances oxidative stress and leads to the opening of the Mitochondrial Permeability Transition pore (MPT pore) [13]. This process causes the collapse of the membrane potential, cessation of ATP synthesis, and rupture of the outer mitochondrial membrane with the release of endonucleases (AIF, EndoG), which fragment nuclear DNA [14]. All this contributes to the development of the cytolytic syndrome.

Mitochondrial dysfunction, in turn, leads to the release of DAMP molecules (Damage-Associated Molecular Patterns): mitochondrial DNA and nuclear fragments, which cause the development of aseptic inflammation and the recruitment of neutrophils, intensifying liver damage. The imbalance between pro-oxidant and antioxidant systems, against the background of the depletion of the enzymatic and non-enzymatic links of antioxidant defense, occurs not only against the background of mitochondrial dysfunction but also nitrosative stress [15]. The initiation of these processes, in turn, leads to the uncontrolled intensification of lipid peroxidation (LPO) in cellular structures. The

accumulation of toxic lipoperoxidation products causes the destabilization of the lipid bilayer of hepatocyte membranes, and a critical violation of their barrier function is one of the key links in the realization of paracetamol's hepatotoxic effect [15].

Also, in conditions of low glutathione levels, prolonged use of even therapeutic doses of paracetamol can lead to the development of pyroglutamic acidosis – a form of high anion gap metabolic acidosis (HAGMA) due to the accumulation of 5-oxoproline (pyroglutamic acid) in the body. Pyroglutamic acidosis is a specific adverse reaction that is unfortunately missed in clinical practice ("chameleon diagnosis") [16].

Furthermore, an increase in the production of NO i O_2^- plays an important role in the pathogenesis of paracetamol-induced hepatitis [17]. Thus, the problem of paracetamol hepatotoxicity and the ways to correct it remain highly relevant. To reduce paracetamol hepatotoxicity, not only general recommendations regarding dosage regimen, frequency, and duration of use, and interaction with other drugs are applied, but also pharmacotherapy. The classic antidote for paracetamol overdose is N-acetylcysteine (NAC). However, its therapeutic window is time-limited (highest efficacy within the first 8–10 hours), and anaphylactoid reactions are possible among its side effects [18].

Therefore, reducing the manifestations of paracetamol hepatotoxicity is a highly relevant task of modern hepatology. Drugs of both synthetic and plant origin are widely used for the pharmacocorrection of drug-induced liver injuries. Given the key role of free radical processes in the pathogenesis of paracetamol liver injury, the pathogenetically justified direction for pharmacocorrection is the use of agents with pronounced antioxidant and membrane-stabilizing potential in complex therapy [19]. Plant hepatoprotectors – Silibor, Hofitol, Phosphogliv, and others [19, 20, 21], which have cytoprotective and antioxidant properties, are widely used in the treatment of liver diseases.

Compared to NAC, polyphenols and other antioxidants included in these herbal remedies are effective for correcting "late" oxidative stress when acetylcysteine is already less effective (after 24 hours) [22].

Lingonberry (*Vaccinium vitis-idaea* L.) is a promising medicinal plant raw material for creating drugs to treat hepatobiliary pathology. Our attention as a potential hepatoprotector was drawn to the fruits and leaves of lingonberry. According to the literature, lingonberry fruits are rich in anthocyanins (cyanidin-3-galactoside) and effectively prevent the development of Non-Alcoholic Fatty Liver Disease (NAFLD) against the background of a high-fat diet [23]. The leaves of *Vaccinium vitis-idaea* L. are traditionally used as a uroseptic, but its phytochemical profile (arbutin, flavonoids, proanthocyanidins) indicates significant hepatoprotective potential that remains insufficiently studied in the context of DILI [24, 25]. Thus, due to their unique phytochemical profile, lingonberry extracts can be electron donors, inactivate reactive oxygen species, and break the chain reactions of peroxidation. This creates the scientific basis for studying the hepatoprotective efficacy of lingonberry extracts as means of leveling the toxic effects of paracetamol and correcting metabolic liver disorders [26].

To enhance the effectiveness of phytoextracts, their modification with amino acids, especially L-arginine, is often applied. L-arginine, on the one hand, can increase the solubility of poorly soluble flavonoids, and on the other hand, literature data indicate that L-arginine is capable of reducing the manifestations of oxidative stress by modulating the activity of superoxide dismutase [26, 27, 28]. It also inhibits the transformation of Ito cells into myofibroblast-like cells, which slows down the processes of fibrosis in chronic liver injuries.

In works [29, 30], convincing evidence is presented for the usefulness of modifying plant extracts with amino acids, including arginine.

AIM OF THE STUDY

The aim of the study was to investigate the effect of native and L-arginine-modified thick extracts of cowberry leaves on the state of the antioxidant system under conditions of acute paracetamol-induced hepatitis in rats.

MATERIALS AND METHODS

The study was conducted at the Central Research Laboratory of the Educational and Scientific Institute of Applied Pharmacy (ESIPA) of the National University of Pharmacy. The study was performed on 36 white outbred rats weighing 180-220 g. The experimental animals were housed in the vivarium of ESIPA on a standard diet with free access to water under typical 12-hour "day-night" cycle conditions. Paracetamol-induced hepatitis in rats was modeled by the intragastric administration of paracetamol at a dose of 750 mg/kg for 2 days [31, 32].

Thick extracts were obtained from the leaves and fruits of common lingonberry at the Department of General Chemistry by PhD, assistant Maslov O.Yu. and PhD, associate professor Komissarenko M. A. under the supervision of the Head of the Department of General Chemistry of NUPh, Professor, D. Sc. Pharm. Kolisnyk S. V. The Thick Lingonberry Leaf Extract (TLLE) contained a sum of catechins (epicatechin, (+)-catechin), a sum of flavonoids (rutin, quercetin), a sum of hydroquinone derivatives (arbutin), a sum of hydroxycinnamic acids (chlorogenic and caffeic acid), and a sum of organic acids (citric and succinic acid). The standardization of the common lingonberry leaf extract was performed by spectrophotometric method, based on the content of the sum of phenolic compounds and the content of the sum of catechins.

The Modified Lingonberry Leaf Extract (MLLE) contained a sum of catechins (epicatechin, (+)-catechin), a sum of flavonoids (rutin, quercetin), hydroquinone derivatives (arbutin), and L-arginine. The standardization of the extract was performed by spectrophotometric method, based on the content of the sum of catechins.

As comparison drugs, silymarin at a dose of 100 mg/kg ("Silibor," 35 mg tablets, manufactured by LLC "Pharmaceutical Company "Zdorovye," Ukraine) [31] and the dietary supplement "Argiclin," manufactured by LLC "ZDRAVOFARM," which contains L-arginine 740 mg and pomegranate polyphenols, were used.

The experimental animals were divided into VI groups of 6 animals each: I – intact control (IC); II – control pathology (CP); III – CP + TLLE; IV – CP + MLLE; V – CP + Silibor. VI – CP + Argiclin.

TLLE, MLLE, and comparison drugs were administered for 5 days prior to paracetamol administration and during 2 days of pathology modeling (1 hour before and 2 hours after paracetamol application) [31]. The substances were administered at a dose equivalent to 13 mg/kg of catechins.

All studies were performed in accordance with the generally accepted provisions of bioethics when working with experimental animals and the requirements of current legislation [33]. After the experiment, the animals were removed from the study under conditions of euthanasia under thiopental anesthesia; blood serum was obtained, and the liver was isolated for further biochemical studies. As a marker of the intensity of Free Radical Oxidation (FRO) processes in the liver, the level of 8-isoprostane was investigated by enzyme-linked immunosorbent assay (ELISA) using 8-Isoprostanr ELISA reagent kits from IBC, Humburg. The content of oxidized glutathione (GSSG) and reduced glutathione (GSH) in the liver was determined spectrophotometrically by the method of V. S. Asatiani. Catalase activity was assessed by the method of Bach [34, 35].

All factual material was processed by methods of variational statistics using parametric and non-parametric analysis methods. The accepted level of significance was $p < 0.05$. The standard software package "Statistica Application" was used to obtain statistical conclusions.

The results of the experiment are shown in Figures 1 and 2.

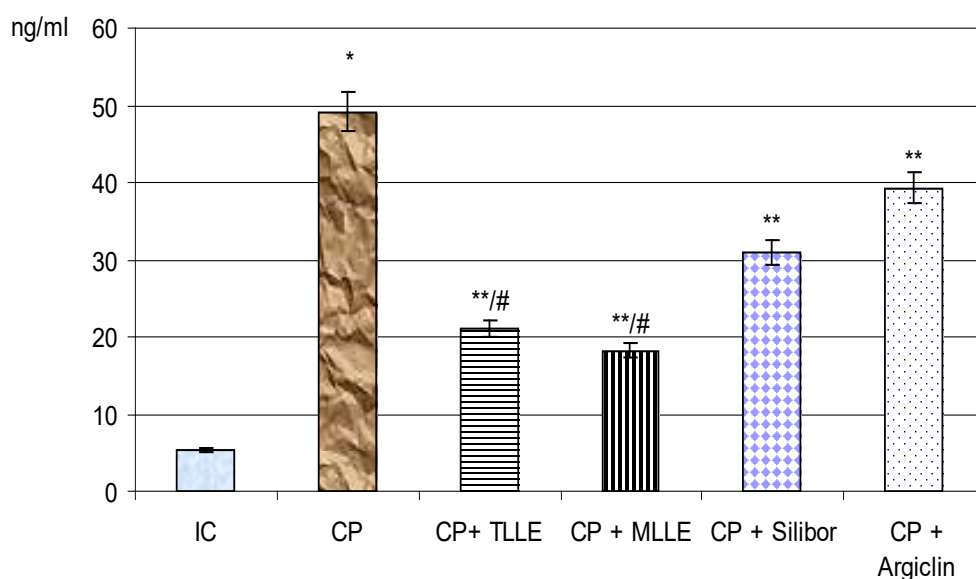


Fig. 1. Changes in the level of 8-isoprostane in the liver of rats with paracetamol-induced hepatitis following treatment with native and L-arginine-modified lingonberry leaf extract

Notes:

1. * - $p \leq 0.05$, statistically significant with respect to the values of IC;
2. ** - $p \leq 0.05$, differences are statistically significant with respect to the values of CP;
3. # $p \leq 0.05$, differences are statistically significant with respect to the values statistically significant with respect to the values of Silibor.

As evidenced by the experimental data, in conditions of paracetamol-induced liver injury in the untreated control group, compared to intact animals (Fig. 1), the liver content of the marker of non-enzymatic phospholipid oxidation of cellular biomembranes - 8-isoprostane - increased by 8.8 times ($p < 0.05$).

Against the background of paracetamol-induced hepatitis, an imbalance was observed in the experimental animals between the content of the oxidized form of glutathione (GSSG), the level of which increased by 2.67 times, and a decrease in GSH by 2.0 times ($p < 0.05$). Furthermore, liver catalase activity decreased by 1.62 times ($p < 0.05$).

All these changes convincingly indicate a significant failure of the liver's antioxidant defense system during paracetamol-induced liver injury.

The administration of native (TLLE) and L-arginine-modified (MLLE) lingonberry leaf extracts to the animals in a treatment and prophylactic regimen significantly decreased the liver GSSG level by 1.2 times and 1.44 times, respectively ($p < 0.05$), and increased the liver GSH content by 1.43 times and 1.67 times, respectively. Catalase activity increased by 1.4 times with the application of TLLE and by 1.58 times with the use of MLLE, respectively.

The level of 8-isoprostane following the use of TLLE (Native Thick Lingonberry Leaf Extract) and MLLE (Modified Lingonberry Leaf Extract) decreased by 2.18 times and 2.5 times, respectively, compared to the untreated control animals (Fig. 1).

When using the comparison drug Silibor, the level of 8-isoprostane decreased by 1.36 times, the

GSSG content decreased by 1.2 times, and the GSH level increased by 1.35 times ($p < 0.05$). Catalase activity increased by 1.22 times. When using the preparation "Argiclin," the level of 8-isoprostane in the liver decreased by 1.7 times ($p < 0.05$), the GSSG level decreased by 1.21 times, the GSH level increased by 1.5 times, and catalase activity increased by 1.3 times (Fig. 2).

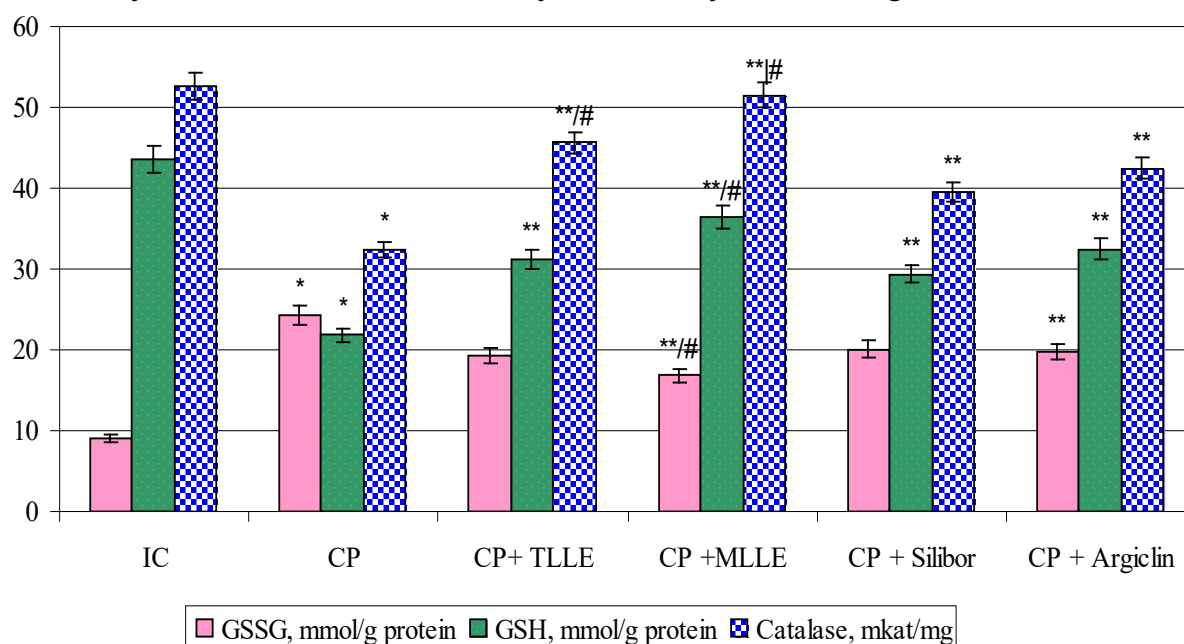


Fig. 2. Effect of native and L-arginine-modified thick extracts of lingonberry leaves on catalase activity and the content of oxidized (GSSG) and reduced (GSH) glutathione in the liver of rats with paracetamol-induced hepatitis

Notes:

1. * - $p \leq 0.05$, statistically significant with respect to the values of IC;
2. ** - $p \leq 0.05$, differences are statistically significant with respect to the values of CP;
3. # $p \leq 0.05$, differences are statistically significant with respect to the values statistically significant with respect to the values of Silibor.

Thus, we have experimentally established the presence of antioxidant properties in both native and L-arginine-modified lingonberry leaf extracts. By the degree of inhibition of free radical oxidation processes and the preservation of the functional activity of the hepatocyte antioxidant compartment, the L-arginine-modified lingonberry leaf extract outperformed the comparison drugs (by 1.7 times against Silibor, $p \leq 0.05$, and by 2.1 times against Argiclin, $p \leq 0.05$) and the native lingonberry leaf extract. The efficacy of the native lingonberry leaf extract compared to the comparison drugs was higher regarding the marker of free radical oxidation (8-isoprostane) and catalase, and comparable or slightly superior regarding the glutathione system.

In our opinion, the more pronounced hepatoprotective effect of the native and L-arginine-modified lingonberry leaf extracts can be explained by the complex influence of the components of these agents on free radical oxidation processes and the state of the antioxidant system. The constituent components of lingonberry leaf extracts are catechins (especially epigallocatechin gallate, EGCG) and hydroquinone derivatives (arbutin), which are powerful hydrogen/electron donors.

They are capable not only of neutralizing ROS (superoxide anion radical, hydroxyl radical) generated by mitochondria against the background of the mentioned pathology but also of hindering free radical destruction of cellular and subcellular hepatocyte structures. Catechins also contribute to the increase in the level of reduced glutathione (GSH) (which was confirmed in our

studies), which allows for the enhancement of detoxification processes in hepatocytes concerning the hepatotoxic metabolite NAPQI [36].

We have also established the positive effect of the studied extracts on liver catalase activity, which also strengthens the endogenous defense of hepatocytes against oxidative stress.

A number of researchers believe that catechins can inhibit the activity of CYP2E1 and CYP3A enzymes, which are responsible for the formation of the toxic metabolite NAPQI. This mechanism reduces the amount of toxic NAPQI formed during paracetamol metabolism [37, 38].

There are also publications regarding the hepatoprotective effects of arbutin [39, 40]. Thus, the synergistic effect of these biologically active components of the lingonberry leaf extract provides protection for hepatocytes against oxidative stress and inflammation caused by NAPQI and subsequent mitochondrial dysfunction.

Scientific publications also contain data that, under conditions of toxic liver damage, there is a depletion of the L-arginine pool and a decrease in the activity of the cytosolic enzyme arginase type I and the mitochondrial arginase type II. The impairment of the activity of these enzymes leads not only to a further increase in intoxication but also intensifies hypoxia and impaired blood flow in the hepatic sinusoids [41].

Therefore, the addition of L-arginine not only allows for the improvement of microcirculation but also enhances the antioxidant properties of the lingonberry leaf extract. Publications in recent years indicate that the use of L-arginine under conditions of toxic liver damage contributes to an increase in NO· levels to physiological indicators. Through reactions with Fe²⁺ in a number of heme-containing proteins (Cytochrome P450, xanthine oxidase, myeloperoxidase, catalase, etc.), NO· inhibits the formation of cytotoxic radicals and improves the functional state of the liver [41].

We associate the higher antioxidant activity of the modified lingonberry extract compared to the traditional hepatoprotector Silibor, which we discovered during the study, with the differences in molecular targets and mechanisms of antioxidant effect realization [42]. The antioxidant effect of the drug Silibor is due to the interaction of silybinin with free radicals in the liver and their conversion into less toxic compounds. This interrupts the LPO-oxidation process of lipids, which prevents the destruction of cellular structures.

Thus, the results obtained indicate the expediency of further research into the prospects of using lingonberry preparations, especially modified with L-arginine, in the complex therapy of hepatobiliary system injuries.

CONCLUSIONS

1. The presence of an antioxidant effect in the native thick and L-arginine-modified cowberry leaf extracts under conditions of paracetamol-induced liver injury has been experimentally proven, which is confirmed by a significant ($p \leq 0.05$) reduction in the level of 8-isoprostane, an increase in the pool of reduced glutathione, a decrease in the level of oxidized glutathione, and an increase in catalase activity.

2. Regarding the effect on reducing the level of 8-isoprostane, the L-arginine-modified cowberry leaf extract significantly ($p \leq 0.05$) outperformed the effect of the comparison drugs, Silibor and Argiclin.

3. Regarding the effect on the parameters of the glutathione system and catalase, the efficacy of the L-arginine-modified cowberry leaf extract significantly ($p \leq 0.05$) exceeded the effect of the comparison drugs, Silibor and Argiclin.

4. The obtained data indicate the prospects for further in-depth studies of the hepatoprotective action of the L-arginine-modified thick extract of cowberry leaves.

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Надійшла 26.09.2025

Прийнята до друку 04.12.2025

Опублікована 09.12.2025

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Вплив нативних та модифікованих екстрактів листя брусниці (*Vaccinium vitis-idaea* L.) на стан процесів вільнорадикального окислення за умов парацетамол-індукованого гепатиту у щурів

Анотація. Одним із найвживаніших безрецептурних препаратів у світі є парацетамол (N-ацетил-пара-амінофенол або ацетамінофен). Цей препарат широко застосовується для симптоматичного лікування головного, м'язового, суглобового, зубного, менструального болю, а також як жарознижувальний засіб при гострих респіраторних інфекціях тощо. Проте тривале застосування парацетамолу або застосування його у високих дозах може призвести до

розвитку гепатиту та гострої печінкової недостатності. Для профілактики та терапії таких уражень печінки, окрім ацетилцистеїну, часто застосовують гепатопротектори, у тому числі й рослинного походження. Метою дослідження стало вивчення впливу нативного та модифікованого L-аргініном густих екстрактів листя брусниці на стан антиокислювальної системи за умов гострого парацетамолового гепатиту у щурів. Встановлено, що застосування нативного густого та модифікованого L-аргініном екстрактів листя брусниці достовірно ($p \leq 0,05$) зменшує рівень 8-ізопростану, збільшує пул відновленого глутатіону, зменшує рівень окисленого глутатіону, а також збільшує активності каталази. За впливом на зниження рівня 8-ізопростану модифікований L-аргініном екстракт листя брусниці достовірно ($p \leq 0,05$) перевищував ефект препарату порівняння Силібор та Аргіклін. За впливом на показники системи глутатіону та каталази ефективність модифікованого L-аргініном екстракту листя брусниці достовірно ($p \leq 0,05$) перевищувала ефект препарату порівняння Силібор та Аргіклін. Вочевидь, гепатопротекторні властивості екстрактів зумовлені комплексним впливом суми катехинів, гідрохінонпохідних, гідроксикоричних кислот та флавоноїдів, яким притаманні антиоксидантні та цитопротекторні властивості. Отримані дані свідчать про перспективи подальших поглиблених досліджень гепатопротекторної дії густого екстракту листя брусниці, модифікованого L-аргініном.

Ключові слова: парацетамоловий гепатит; екстракт листя брусниці; перекисне окиснення ліпідів; гепатопротекторна активність; антиоксидантна активність; щури; L-аргінін.

Автори заявляють про відсутність конфлікту інтересів. [The authors declare no conflict of interest.]

Цитування (ДСТУ):

Деримедвідь Л. В., Петрошчук С. Р. Вплив нативних та модифікованих екстрактів листя брусниці (*Vaccinium vitis-idaea* L.) на стан процесів вільнорадикального окислення за умов парацетамол-індукованого гепатиту у щурів. *Лікарська справа*. 2025. № 4. С. 165–175. <https://doi.org/10.31640/LS-2025-4-18>

Citation (APA):

Derymedvid, L. V., & Petroshchuk, S. R. (2025). The effect of native and modified lingonberry leaf extracts (*Vaccinium vitis-idaea* L.) on the state of free radical oxidation processes under conditions of paracetamol-induced hepatitis in rats. *Likars'ka Sprava*, (4), 165–175. <https://doi.org/10.31640/LS-2025-4-18>