UDC 615.322:615.254.7: 16.61-002:599.323.4
DOI: 10.15587/2519-4852.2024.314121

INVESTIGATION OF THE INFLUENCE OF THE EXTRACT OF THE HERB OF UMBELLATE WINTERGREEN ON THE STRUCTURAL AND FUNCTIONAL STATE OF THE KIDNEYS OF RATS

Oleksiy Kovregin, Yulia Laryanovska, Tetiana Yudkevych, Dmytro Lytkin, Iryna Lebedinets, Inna Vladymyrova

Experimental studies were carried out as part of a preclinical study of the umbellate wintergreen herb extract regarding the possibility of using the phytoremedical agent in diseases of the kidneys and urinary tract.
The aim. *Study of the effect of umbellate wintergreen herb extract on the structural and functional state of kidneys in rats.*
Materials and methods. *The kidneys of rats were studied after: a single subcutaneous injection of 2.5 % potassium chromate solution at a dose of 0.7 ml/kg on the first day of the experiment – control pathology; administration of an alcoholic extract of the umbellate wintergreen herb (UWH) at a dose of 3 ml/kg or a reference preparation of a solution of lespefril at a dose of 3 ml/kg starting from the second day of the experiment (after the induction of renal failure) daily for 20 days in the form of aqueous solutions prepared on a physiological solution; intact rats that received an equivalent amount of physiological solution.*
The following morphological indicators were used to assess the condition of the renal corpuscles: degree of expansion of the Shumlyansky-Bowman capsule, mesangium; segmental intracapillary proliferation. The degree of expressiveness of atrophy, edema, vacuolar dystrophy and disorganization of the nephrothelium, tubulohidrosis was evaluated.
Results. *After treatment with umbellate wintergreen extract in rats with chromate-induced renal failure, more preservation of the cytoarchitectonics of the renal tissue was observed. In most of the renal corpuscles, the size of the urinary space is clearly reduced. In the vascular glomeruli, as a rule, the pattern of the capillary network is clear, the thickening of the BM of the capillaries is not observed. The saturation of mesangial and endothelial cells in most glomeruli is close to the intact control. In general, the expressiveness of changes in the glomerular apparatus in rats after administration of UWH decreased by 44.87 % compared to rats with renal failure that were not treated with the extract.*
Conclusions. *The extract of the umbellate wintergreen herb helps to protect the morphostructure of the kidney tissue of rats with chromate-induced renal failure, reducing the degree of damage to the renal corpuscles and tubules. In terms of the expressiveness of its nephroprotective properties, the extract of umbellate wintergreen was inferior to the reference drug Lespefril solution in its effect on the state of the glomerular apparatus and ahead of it in its effect on the state of the tubular system.*
After treatment with the extract in rats with chromate-induced renal failure, more preservation of the cytoarchitectonics of the renal tissue was noted. In most of the renal corpuscles, the size of the urinary space is clearly reduced. In the vascular glomeruli, as a rule, the pattern of the capillary network is clear, the thickening of the BM of the capillaries is not observed. The saturation of mesangial and endothelial cells in most glomeruli is close to the intact control
Keywords: *chronic kidney disease, Chimaphila umbellata (L.), nephroprorectory effect, phytotherapy*

How to cite:
Kovregin, O., Laryanovska, Y., Yudkevych, T., Lytkin, D., Lebedinets, I., Vladymyrova, I. (2024). Investigation of the influence of the extract of the herb of umbellate wintergreen on the structural and functional state of the kidneys of rats. ScienceRise: Pharmaceutical Science, 5 (51), 89–95. http://doi.org/10.15587/2519-4852.2024.314121

1. Introduction

Herbal remedies have a positive effect on diseases of the kidneys and urinary organs [1]. Long-term use of medicinal plants makes it possible not only to relieve inflammatory processes, to achieve a positive effect, but also to a certain extent to restore the lost or impaired functions of the kidneys and urinary tract [2].

The peculiarities of the effect of medicinal plants on the body and their advantages are that they are quickly and actively included in biochemical processes [3], have a mild but complex effect, have a positive effect on metabolism and, in general, rarely cause complications [4]. This is usually due to the insignificant toxicity of medicinal plants and relative biological safety for the body [5, 6]. Herbal preparations also have specific features of action, namely: due to the presence in plants of numerous biologically active substances with various pharmacological activities, they can be used for the treatment of multisystem pathologies [7].

Chimaphila umbellata (L.) – perennial herbaceous plant that has diuretic, astringent, pain-relieving and other effects; and can treat various kidney and urinary tract con-

ditions. Arbutin glycoside, tannins (up to 5 %), flavonoids, tannins, a bitter substance (ursone), organic acids, gums, resins, and mucilage are found in the grass of the umbellate wintergreen. The herb also contains sitosterol, quinine and gallic acids, methyl ester of salicylic acid, vitamins, trace elements and other biologically active substances [8].

In this aspect, it is important to study not only the effectiveness, but also the safety of herbal medicines [9]. Therefore, the study of the effect of the umbellate wintergreen extract on the structural and functional state of the kidneys of rats is a continuation of the study of the nephroprotective effect of this phytotherapeutic agent.

2. Planning (methodology) of research

For the research, we used the dried grass of the umbellate wintergreen (producer of TM "Zelena Apteka", Zhytomyr). Wintergreen extract was obtained based on the Research Plant "HNCLS" (Kharkiv) in the period May–June 2023. The umbellate wintergreen extract (UWH) was obtained with 50 % ethyl alcohol, which is presented in detail in the article [10].

The study was performed on 60 outbred sexually mature rats (males), weighing 250±20 g, which were kept in the vivarium of the ESTC MBK of the National Academy of Sciences. After acclimatization, the experimental animals were evenly divided into 6 experimental groups of 10 animals each. The extract was administered intragastrically on an empty stomach once a day using a special metal probe for intragastric administration [11].

The experiment was conducted in several stages.

Stage I: study of rat kidneys after:

– a single subcutaneous injection of 2.5 % potassium chromate solution at a dose of 0.7 ml/kg on the first day of the experiment – control pathology;

– the administration of the alcohol extract of the umbellate wintergreen herb (UWH) at a dose of 3 ml/kg or the reference preparation of the lespefril solution at a dose of 3 ml/kg starting from the second day of the experiment (after the induction of renal failure) every day for 20 days in the form of aqueous solutions prepared on a physiological solution;

– intact rats that received an equivalent amount of physiological solution.

Stage II: removal of animals from the experiment (carried out 20 days after the start of treatment).

Stage III: preparation of kidney samples for the study of the structural and functional state:

– fixed in 10 % formalin solution;

– dehydrated in alcohols of increasing strength;

– poured in paraffin;

– the sections were stained with hematoxylin and eosin, and the PAS reaction was performed.

Stage IV: conducting a semi-quantitative (score) assessment of damage to the renal corpuscles and cortical tubules. The following morphological indicators were used to assess the state of the renal corpuscles:

– degree of expansion of the Shumlyansky-Bowman capsule, mesangium;

– segmental intracapillary proliferation in 10 renal bodies in each studied rat;

– degree of expressiveness of atrophy, edema, vacuolar dystrophy and disorganization of nephrothelium, tubulohidrosis.

3. Materials and methods

The experiment was conducted in June–August 2024.

Kidneys of rats were studied after:

– a single subcutaneous injection of 2.5 % potassium chromate solution at a dose of 0.7 ml/kg on the first day of the experiment – control pathology;

– the administration of the alcohol extract of the umbellate wintergreen herb (UWH) at a dose of 3 ml/kg or the reference drug lespefril solution at a dose of 3 ml/kg starting from the second day of the experiment (after the induction of renal failure) daily for 20 days in the form of aqueous solutions prepared on a physiological solution;

– intact rats that received an equivalent amount of physiological solution.

Studies were conducted on sexually mature rats (males). Animals were kept in a separate room with controlled microclimate parameters, in plastic cages with individual ventilation. The room was sterilized daily using a UV lamp. Animals had free access to water. Granulated balanced feed was used to feed the animals.

The study was conducted in accordance with the Law of Ukraine "On Medicinal Products" and in accordance with the requirements of the SEC of Ministry of Health of Ukraine regarding preclinical studies, taking into account the provisions of Directive 86/609/EU of the European Parliament and the Council of the EU dated November 24, 1986 "On the convergence of laws, regulations and administrative provisions of the EU states on the protection of animals used for experimental and other scientific purposes", Directive of the European Parliament and the Council of the EU 2010/63/EU of September 22, 2010 "On the protection of animals used for scientific purposes" (Protocol of the Commission on of bioethics of the National Academy of Sciences No. 9 dated May 3, 2023) [12, 13].

Withdrawal from the experiment was carried out 20 days after the start of treatment. Kidney samples were fixed in 10 % formalin solution, dehydrated in alcohols of increasing strength, embedded in paraffin. Sections were stained with hematoxylin and eosin, and the PAS reaction was performed [12]. A semi-quantitative (score) assessment of damage to the renal corpuscles and cortical tubules was carried out. The following morphological indicators were used to assess the condition of the renal corpuscles: degree of expansion of the Shumlyansky-Bowman capsule, mesangium; segmental intracapillary proliferation (0 – no changes; 1b – weak changes; 2b – moderate changes; 3b – pronounced changes) – in 10 kidney bodies in each studied rat. The results for each body were summed up, the average indicator for 10 bodies was derived [13–15]. Tubule damage was assessed in 5 p/s of the cortical layer and the cortico-medullary zone, which did not overlap. The degree of expressiveness of atrophy, swelling, vacuolar dystrophy and disorganization of nephrothelium, tubulohidrosis was evaluated: 0 – no changes; 1b – damage to 10 % of tubules; 2b – damage

to 25 % of tubules; 3b – damage to 50 % of tubules; 4b – damage to 75 % of tubules; 5b – damage to more than 75 % of tubules. The results of the measurements were summarized for each test sample, and the average indicator was derived [16, 17].

Kidney micro-preparations were examined under a Granum light microscope (Granum, China), photomicrographs of microscopic images were carried out with a Granum DSM 310 digital video camera (Granum, China). Photographs were processed on a Pentium 2.4 GHz computer using the Levenhuk 310 Toup View program.

Digital data were processed statistically. Standard deviation /median and upper and lower quartiles, minimum and maximum value. Non-parametric methods (Kruskal-Wallis and Mann-Whitney test) were used for sampling.

4. Research results

In intact rats, renal corpuscles are normal in size and density in the cortical substance. The pattern of glomerular capillary loops is normal in expression, cellular saturation; capillaries are moderately full-blooded. The lumen of the Shumlyansky-Bowman capsule is normal. The size and shape of the distal and proximal parts of the tubules of the nephrons corresponded to the norm. The epithelium lining the tubules was not changed. The nuclei of the cells were clearly contoured, the apical part of the cells was moderately fluffed, the lumen of the tubules was not spread. Straight tubules and collecting tubules of the brain layer are not changed. There were no violations of the intertubular stroma in the cortex and medulla (Fig. 1).

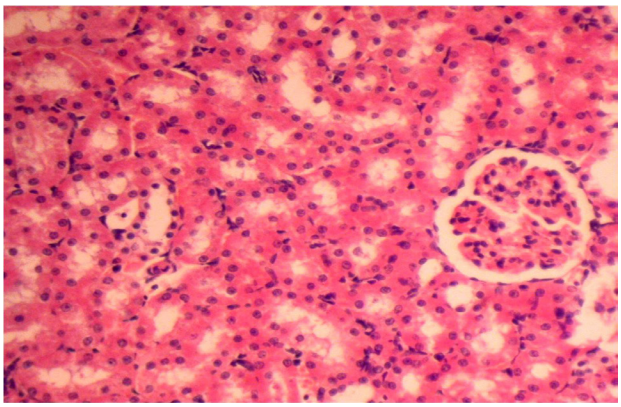
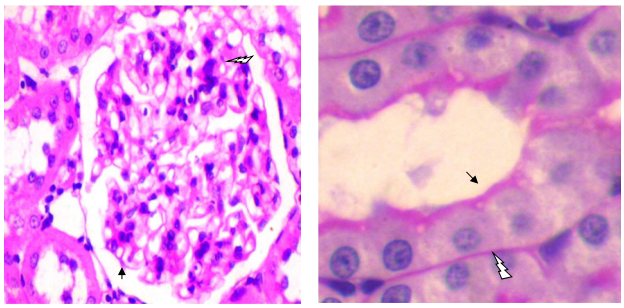


Fig. 1. Kidney of an intact rat: the normal state of the renal corpuscle and convoluted tubules. Hematoxylin-eosin (×200)

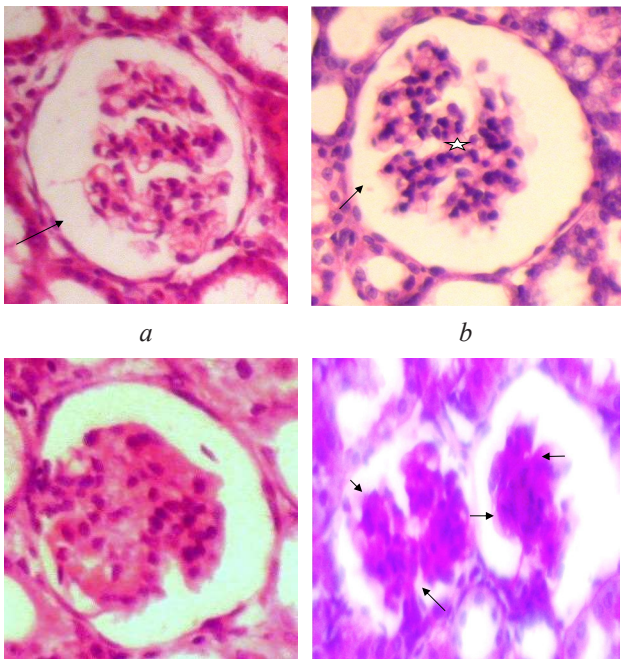
PAS-staining of the sections showed that the BM of the glomerular capillaries was not thickened, and the mesangial space was not expanded. The brush border and BM of the tortuous tubules of the nephrons are unchanged (Fig. 2).

20 days after subcutaneous administration of potassium chromate, many renal corpuscles with marked hydroectasia of the capsule were found in the glomerular system of rats of the CP group. In the part of the glomeruli, the division of the glomerulus into separate parts (lobularity), the collapse of the capillary network, the thickening of the BM of the capillaries, the expansion of the mesangium due to the accumulation of PAS-positive material, and the proliferation of mesangial and epithelial cells were noted (Fig. 3).



a *b*

Fig. 2. Kidney of an intact rat: *a* – basal membranes (black arrow) of glomerular capillaries are not thickened, mesangial space (white arrow) is not expanded (×400); *b* – brush border (black arrow) and basal membranes (white arrow) of convoluted tubules of nephrons without changes (immersion). PAS-reaction according to McManus

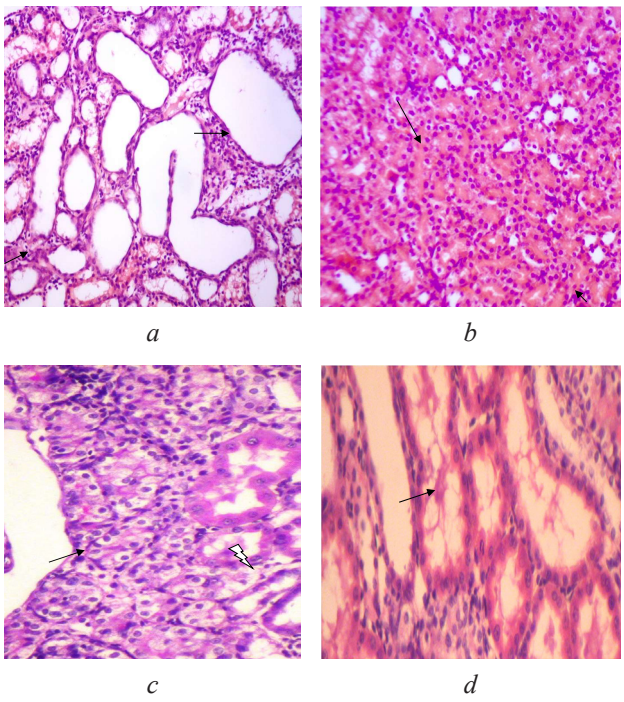


a *b* *c* *d*

Fig. 3. Rat kidney after the introduction of potassium chromate: *a* – hydroectasia of the Shumlyansky-Bowman capsule (arrow); *b* – lobule glomerulus, proliferation of mesangium cells (asterisk); *c* – fall of the capillary network; *d* – expansion of the mesangium, accumulation of PAS-positive material (arrows). *a*–*c* – hematoxylin-eosin; *a, b* – ×250, *c* – ×400; *d* – McManus PAS reaction, ×400

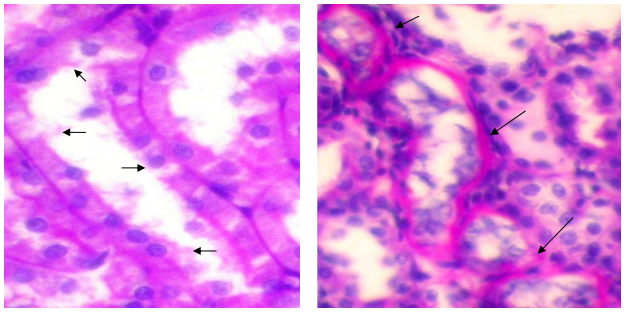
In the tubular system, a significant part of the tubules of the cortical layer is dilated – tubulohidrosis of varying degrees of expressiveness. The nephrothelium is flattened, sometimes in a state of atrophy. In a number of tubules, the nephrothelium is partially or completely disorganized, the cells are dystrophically changed (vacuolization). Part of the tubules contained hyaline cylinders. Quite often, the epithelium of the tubules (mainly the cortico-medullary zone) is swollen, the lumen of the tu-

bules is not visualized (Fig. 4). The basal membrane of the tubules is fragmented, the thyroid border is destroyed (Fig. 5). The obtained microscopic picture is characteristic of the state of renal failure and is confirmed by the data of the literature [15].



a *b* *c* *d*

Fig. 4. Rat kidney after administration of potassium chromate: *a* – tubulohidrosis, flattening, atrophy of the epithelium (arrows, ×100); *b* – swelling of the epithelium, absence of lumen of tubules (×200); *c* – vacuolization, disorganization of the epithelium (×250); *d* – hyaline cylinders in the lumen of tubules (×250). Hematoxylin-eosin



a *b*

Fig. 5. Rat kidney after the introduction of potassium chromate: *a* – fragmentation of the brush border; *b* – BM part of the tubules is absent, in some – thickened, loose. PAS-reaction according to McManus, ×400

Focal, not sharply defined, lymphohistiocytic infiltration of the interstitium of the cortical substance was noted. Moderate tubulohidrosis of straight tubules, focal atrophy of nephrothelium was observed in the medulla.

A semi-quantitative assessment of the pathological changes in the renal corpuscles and cortical tubules of the nephron of rats in the conditions of chromate-induced renal failure is presented in Table 1.

Table 1

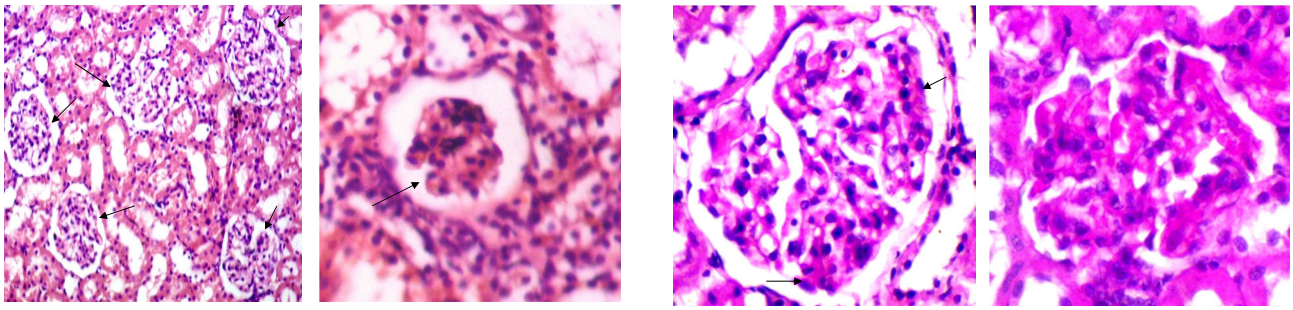
Morphometric indicators of the condition of the glomerular and tubular structures of the kidneys of rats with chromate-induced renal failure and when it is corrected with the extract of umbellate wintergreen, scores

Morphological indicators	Experimental group			
	Intact control	Control pathology	Extract of umbellate wintergreen	Lespefril solution
Renal bodies: hydroectasia of the capsule, expansion of the mesangium, roliferation of mesangial-endothelial cells	0	7.8	4.3	3.6
Cortical tubules: tubulohidrosis, atrophy, disorganization, vacuolization of cells	0	14	9.6	12.0

After treatment with UWH in rats with chromate-induced renal failure, more preservation of renal tissue cytoarchitectonics was observed. In most of the renal corpuscles, the size of the urinary space is clearly reduced. In the vascular glomeruli, as a rule, the pattern of the capillary network is clear, the thickening of the BM of the capillaries is not noticed. The saturation of mesangial and endothelial cells in most glomeruli is close to the intact control. Expansion of the mesangium, accumulation of PAS-positive material in it was either not noted, or the expressiveness of these indicators was inferior to CP. In part of the glomeruli, the division into separate parts ("lobularity") was preserved, in single glomeruli, a drop in the capillary network was observed (Fig. 6). In general, the expressiveness of changes in the glomerular apparatus in rats after administration of UWH decreased by 44.87 % compared to rats with renal failure that were not treated with the extract (Table 1).

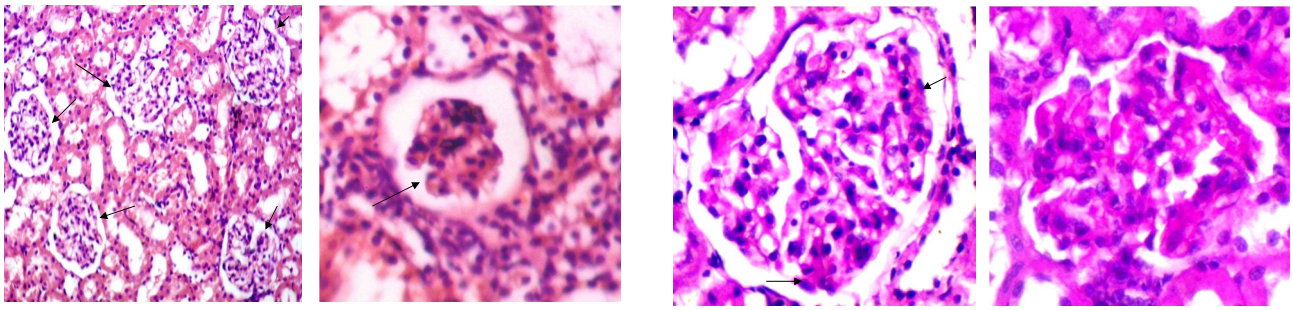
There are no signs of tubulohidrosis in the main mass of cortical tubules. In small areas of the cortico-medullary zone, part of the tubules was expanded, but atrophy of the epithelium was not observed. Basically, signs of moderate swelling of the epithelium, vacuolation of cells without disorganization of the pattern were found. In some zones hyaline cylinders are visible in the lumen of the tubules. The basal membrane of the tubules is not damaged, the thyroid border of the epithelium is somewhat thinned (Fig. 7). According to semi-quantitative assessment, the degree of cortical tubule damage was reduced by 31.4 % compared to untreated rats (Table 1).

Treatment of rats with simulated renal failure with the reference drug lespefril solution clearly improved the condition of the renal corpuscles. There were almost no signs of ectasia of the Shumlyansky-Bowman capsule, the pattern of the capillary network was clear, and no proliferation of mesangial-endothelial cells was detected. The fall of the capillary network was not visualized. Expansion of the mesangium was moderate. BM of capillaries is not thickened (Fig. 8). The expressiveness of changes in renal corpuscles in rats after administration of lespefril solution decreased by 53.85 % relative to CP (Table 1).



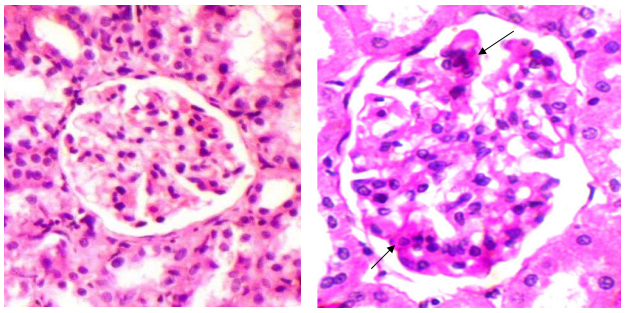
a *b* *c* *d*

Fig. 6. The kidney of a rat with chromate-induced renal failure after treatment with an extract of umbellate wintergreen: *a* – reduction of hydroectasia of the Shumlyansky-Bowman capsule in most of the renal corpuscles (arrows), a clear pattern of the capillary network, moderate saturation of the capillary network with mesangial and endothelial cells (×200); *b* – hydroectasia of the capsule, a drop in the capillary network in a single vascular glomerulus (×250); different expressiveness of the expansion of the mesangium; *c* – finely focused (×400); *d* – diffuse (×400); *a, b* – hematoxylin-eosin; *c, d* – PAS reaction according to McManus



a *b* *c* *d*

Fig. 7. Kidney of a rat with chromate-induced renal failure after treatment with an extract of umbellate wintergreen: *a* – the main mass of cortical tubules without signs of tubulohidrosis, vacuolization of the epithelium without damage to the tissue pattern (×200); *b* – swelling of the epithelium, tubulohidrosis of a part of tubules of the cortico-medullary zone (×250); *c* – hyaline cylinders in the lumen of some tubules (arrows, ×400); *d* – thinning of the brush border, BM of tubules is preserved (immersion). *a–c* – hematoxylin-eosin; *d* – McManus PAS reaction

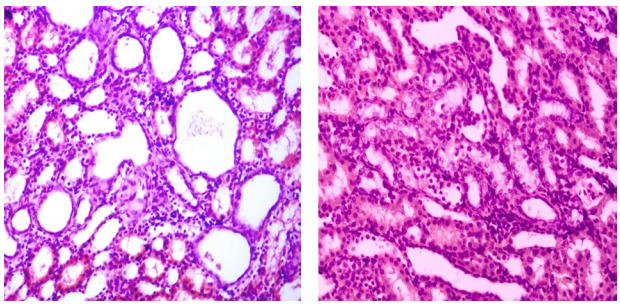


a *b*

Fig. 8. Kidney of a rat with chromate-induced renal failure after treatment with lespefril solution: *a* – renal corpuscle without signs of capsule ectasia, intracapillary proliferation (×250); *b* – expansion of the mesangium within moderate limits (×400). *a* – hematoxylin-eosin; *b* – McManus PAS reaction

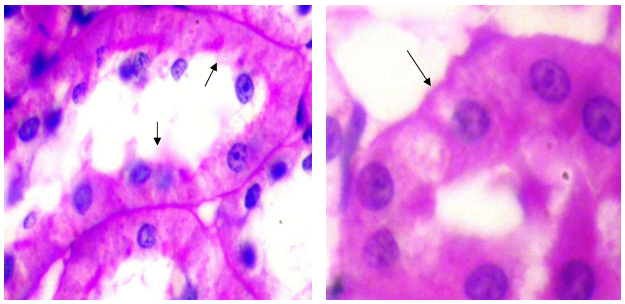
The effect on the condition of the cortical tubules after therapeutic administration of lespefril solution was not as indicative as on the renal corpuscles. Both in the cortical substance and in the cortico-medullary zone, a significant number of tubules showed signs of tubulohidrosis of varying degrees of expressiveness. The epithelium is flattened, vacuolated in parts, swollen. Hyaline cylinders are visible in the lumen of part of the tubules. Microsites of tubule destruction were detected (Fig. 9). All this affected the point assessment of the state of tubules, which was only 14.3 % inferior to CP (Table 1).

Accordingly, the mesh border of the tubules is often damaged, the BM part is thickened (Fig. 10).



a *b*

Fig. 9. Kidney of a rat with chromate-induced renal failure after treatment with lespefril solution: varying degrees of tubulohydrosis (*a* – cortical tubules; *b* – cortico-medullary tubules, ×200), swelling of the epithelium (*c*, ×250), hyaline cylinders in the lumen of the tubules, a microsection (arrow) destruction of tubules (*d*, ×250). Hematoxylin-eosin



a *b*

Fig. 10. Kidney of a rat with chromate-induced renal failure after treatment with Lespefril solution: *a* – looseness, damage to the brush border of the tubule; *b* – fragmentary thickening of the BM. PAS reaction according to McManus, immersion

5. Discussion of research results

Research on the influence of herbal remedies on the structural and functional states of organs and systems of experimental animals is widely used at the stage of preclinical study of herbal remedies [18]. There is rich empirical and experimental experience in the use of phytoniring drugs in the treatment of diseases of the kidneys and urinary system. However, the evidence base is still insufficient. Phytopharmaceuticals are successfully used for the symptomatic treatment of chronic kidney disease, but they are presented in a rather narrow range despite a number of advantages, including a mild therapeutic effect and a much smaller list of side effects [19].

Chimaphila japonica Miq. is a perennial herbaceous plant that has diuretic, astringent, analgesic, and other effects; and it can treat various conditions such as edema, hydrops, etc. At present, little research has been carried out on the chemical composition of the plant; the biological activity is mainly directed towards crude extracts, and the pharmacodynamic material basis is unclear. To date, only a few terpenoids, flavonoids, sterols, quinoids, and phenolic glycosides have been reported. Therefore, an in-depth study of the active ingredients of *C. japonica* is essential. In our continuing search for potent diuretic agents from medicinal plants, petroleum ether (PE), ethyl acetate (EtOAc), and *n*-butyl alcohol (*n*-BuOH) soluble fractions from the 75 % ethanol extract of whole-plant *C. japonica* were evaluated. Herein, the diuretic bioguided isolation of the active *n*-BuOH constituents of the soluble fraction, together with the diuretic activity of some of the isolated compounds, is evaluated and the possible diuretic mechanisms of the active compounds are investigated [20, 21].

Therefore, an urgent practical task is to find ways to expand the indications for already known phytotherapeutic agents and to study the possibility of their use for the treatment of chronic kidney disease.

Practical relevance. The importance and expediency of this study lies in the study of a potential nephroprotective phytotherapeutic agent for use in diseases of the kidneys and urinary tract.

Study limitations. This work did not consider the problems of combined therapy of wintergreen extract with other drugs for the treatment of chronic renal failure.

Prospects for further research. The obtained experimental results are based on biochemical, laboratory, histochemical analyzes and functional indicators of the kidneys. It is also promising to study immunohistochemical evaluation of umbellate wintergreen extract to obtain more convincing evidence.

6. Conclusions

After treatment with the extract in rats with chromate-induced renal failure, more preservation of the cytoarchitectonics of the renal tissue was noted. In most of the renal corpuscles, the size of the urinary space is clearly reduced. In the vascular glomeruli, as a rule, the pattern of the capillary network is clear, the thickening of the BM of the capillaries is not observed. The saturation of mesangial and endothelial cells in most glomeruli is close to the intact control.

Therefore, based on the obtained data, it can be concluded that the umbellate wintergreen herb extract helps to protect the morphostructure of the kidney tissue of rats with chromate-induced renal failure, reducing the degree of damage to the renal corpuscles and tubules. In terms of the expressiveness of its nephroprotective properties, the umbellate wintergreen extract is inferior to the reference drug lespefril solution in its effect on the state of the glomerular apparatus and ahead of it in its effect on the state of the tubular system.

Conflict of interests

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research, and its results presented in this paper.

Funding

The study was performed without financial support.

Data availability

Data will be made available on reasonable request.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the current work.

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Received date 08.08.2024
Accepted date 22.10.2024
Published date 31.10.2024

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