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QUALIFICATION WORK

on the topic: **«STUDY OF THE ANTI-INFLAMMATORY ACTION OF BURDOCK LEAVES THICK EXTRACT»**

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ANNOTATION

An experimental study of the anti-inflammatory properties of a thick extract of burdock leaves was conducted. The obtained results can be used for further preclinical study and the creation of domestic herbal preparations based on a thick extract of burdock leaves for complex therapy of inflammatory diseases.

The work consists of an introduction, the main part (literature review, research methods, own research and their discussion), conclusions, a list of used sources and contains 40 pages, 6 tables, 53 references to literature sources.

Key words: thick extracts of leaves of burdock, anti-inflammatory, anti-exudative, reparative, anti-proliferative effect.

АННОТАЦІЯ

Проведено експериментальне вивчення протизапальних властивостей густого екстракту листя великого лопуха. Отримані результати можуть бути використані для подальшого доклінічного вивчення та створення на основі густого екстракту листя лопуха великих вітчизняних фітопрепаратів для комплексної терапії запальних захворювань.

Робота складається з вступу, основної частини (огляд літератури, методи дослідження, власні дослідження та їх обговорення), висновків, списку використаних джерел та містить 40 сторінок, 6 таблиць, 53 посилання на джерела літератури.

Ключові слова: густий екстракт листя лопуха, протизапальна, антиексудативна, репаративна, антипроліферативна дія.

LIST OF CONTENTS

ABBREVIATION LIST

AFO – active forms of oxygen

BAFS – biologically active food supplement

BAS – biologically active substance

BHPG – benign hyperplasia of the prostate gland

COX – cyclooxygenase

ED_{50} – average effective dose

GIT – gastrointestinal tract

LPO – lipid peroxidation

LT – leukotrienes

min – minutes

MOH – Ministry of Health

NSAID – nonsteroidal anti-inflammatory drugs

NUPh – National University of Pharmacy

PG – prostaglandins

RA – rheumatoid arthritis

SEC – State expert center

WHO – World Health Organization

INTRODUCTION

Relevance of the topic. The problem of pharmacological correction of inflammation, as before, remains an actual, not fully solved problem of modern medicine. Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the groups of drugs that are most often used in clinical practice. The latter is connected with the availability of drugs of this group of a number of pharmacological properties: anti-inflammatory, analgesic, antipyretic, antithrombotic. They are "first-line" drugs for the treatment of inflammatory diseases of the musculoskeletal system. In recent years, the number of NSAIDs in the world has grown rapidly, and currently this group includes many drugs that differ in terms of action and form of release. Given the widespread use of these means, special attention should be paid to their safety issues, since even short-term use can lead to the development of adverse reactions.

In connection with the above, despite the diverse assortment of NSAIDs there is a need for drugs to correct inflammation, the search for new drugs with an unconventional mechanism of action and minimal side effects is urgent and ongoing. One of the promising directions for the creation of safe and effective anti-inflammatory agents are herbal drugs.

In recent years, interest in herbal medicines has increased significantly. Unlike synthetic drugs, they have a milder physiological effect and lower toxicity. It should also be emphasized that medicinal plants differ in the diversity of their chemical composition, which determines the great pharmacodynamic capabilities of herbal drugs.

One of the plants that has been used for many years in traditional medicine for the treatment of inflammatory conditions is burdock large. Burdock roots and leaves are used in the treatment of diseases of the skin, respiratory tract, diseases of the liver, pancreas, stomach ulcers, diseases of the joints, kidneys, etc.

All of the above, as well as the analysis of the phytochemical composition of large burdock leaves, allows us to predict the presence of anti-inflammatory properties in this medicinal raw material. An important advantage of this plant is also a large raw material base. Therefore, the pharmacological study of the anti-inflammatory properties

of the thick extract of burdock leaves with the aim of further creating medicines for the treatment of inflammatory diseases is relevant and promising.

The aim of the study. Experimental study of the anti-inflammatory properties of a thick extract of burdock leaves on adequate models of inflammation in rats.

The objectives of the study:

1. Analysis of the market of modern herbal drugs with anti-inflammatory properties and determination of promising directions for improving the pharmacotherapy of inflammatory diseases.
2. Study of the antiexudative properties of a thick extract of large burdock leaves in a wide range of doses on models of acute aseptic inflammation in rats.
3. Determination of the average effective dose of large burdock leaf extract for further research.
4. Evaluation of the expressiveness of antialterative and reparative properties of burdock leaf extract on the model of acetic acid ulcers in rats.
5. Study of the antiproliferative properties of a thick extract of burdock leaves on the cotton wool granuloma model in rats.
6. Analysis of the obtained data and evaluation of the expediency of further preclinical studies of the anti-inflammatory properties of the thick extract of large burdock leaves.

The study object. Optimizing the therapy of inflammatory diseases.

The study subject. Anti-inflammatory properties of a thick extract of large burdock leaves.

The research methods. Pharmacological, macroscopic, statistical methods.

Practical significance of the obtained results. According to the results of the work, it was established that the thick extract of burdock leaves has anti-exudative, moderate reparative and anti-proliferative properties and can be used in the complex therapy of inflammatory diseases of various genesis. It has been proven that the thick extract of burdock leaves is a promising substance for further in-depth preclinical and clinical study with the aim of creating new domestic drugs with anti-inflammatory properties. The results of the work are highlighted in 2 theses.

Elements of scientific research. For the first time, an experimental study of the anti-inflammatory and reparative properties of a thick extract of burdock leaves was conducted on adequate models of inflammation in rats. It was determined that a thick extract of burdock roots in conditions of acute aseptic inflammation has an anti-exudative effect. The studied extract in a conditionally effective dose of 25 mg/kg does not show an anti-alterative effect, but has moderate reparative properties in conditions of acetic acid ulcers in rats. Burdock leaves extract is inferior to sodium diclofenac and superior to quercetin in its reparative effect on this model. It was also established that the investigated agent exerts a moderate antiproliferative effect on the cotton wool granuloma model.

Approbation of research results and publication. The results of the work were tested at the All-Ukrainian scientific and practical Internet conference with international participation, dedicated to the 30th anniversary of the establishment of the Department of Clinical Pharmacology and Clinical Pharmacy of the National Academy of Sciences «Клінічна фармація в Україні та світі» (16-17 March 2023, Rharkiv) and 2 theses published.

Structure and volume. The work consists of an introduction, the main part (literature review, research methods, own research and their discussion), conclusions, a list of used sources and contains 40 pages, 6 tables, 53 references to literature sources.

CHAPTER 1
ACHIEVEMENTS AND PROBLEMS OF USING MODERN ANTI-INFLAMMATORY AGENTS
(literature review)

1.1. Epidemiology and medico-social significance of inflammatory diseases

Inflammation is a reaction of living tissues to local damage that arose during evolution. It consists in complex changes in the microcirculatory channel, blood system and connective tissue aimed at isolating and eliminating the damaging agent and restoring (or replacing) damaged tissues.

Among the causes of inflammation, there are exogenous (external) factors (microorganisms, protozoa, chemical substances, foreign body, pressure, tears, thermal effects, radiant energy, etc.) and endogenous (internal) factors arising in the body itself as a result of another disease (stones in the gallbladder or urinary bladder, thrombi, antigen-antibody complexes, foci of necrosis, hematoma, etc.). These manifestations of tissue inflammatory response to damage are realized at the level of cells, microcirculation, and connective tissue. Three stages are conventionally distinguished in the pathogenesis of Z.: alteration, exudation, and proliferation [1].

Inflammation begins with cell damage - alteration. A distinction is made between primary and secondary alteration. The primary alteration is the result of the damaging action of the inflammatory factor and depends mainly on its properties. Primary alteration is not yet a component of inflammation, because inflammation is a reaction to damage, that is, to primary alteration. Secondary alteration is the result of exposure to connective tissue, microvessels and blood of lysosomal enzymes released from cells and active oxygen metabolites. That is, secondary alteration is an integral part of the inflammatory process, as it is the body's response to damage. Alteration of cells is accompanied by a violation of the structure and function of intracellular formations. When mitochondria are damaged, respiration is limited or stopped, glycolysis is enhanced, the concentration of macroergic compounds, the activity of the ion pump of the plasma membrane decreases, cells lose K, P, Mg, Ca, and Zn ions. In the focus of

inflammation, tissue hypoxia, metabolic acidosis, hyperonkyia develops, and due to an increase in the number of extracellular molecules, hyperosmia develops. The result of damage to lysosomes is the release of lysosomal enzymes. Alteration of the vascular wall is accompanied by an increase in its permeability. Alteration of nerve formations with impaired impulse conduction through vasoconstrictors leads to neuroparalytic arterial hyperemia. Irritation of nerve elements, for example, receptors, by the axon-reflex mechanism is also manifested by the expansion of arterioles, relaxation of precapillary sphincters with the development of arterial hyperemia. Hypoxia and products of primary alteration initiate secondary alteration. Hypoxia, in turn, induces the activation of lipid peroxidation, but the lysosomal enzymes of neutrophils, macrophages and the contact ("guard") polysystem of blood plasma proteins are of particular importance in the development of secondary alteration. Lysosomal enzymes destroy cell membranes and components of supporting tissue both directly through the action of phospholipase, collagenase, elastase and exoglycosidase, and indirectly through the release of mediators (biogenic amines) by smooth cells, basophils, platelets or through the components of the "guard" system of blood plasma proteins [1, 2].

The stage of alteration is followed by the stage of exudation - the exit of the liquid part of blood, electrolytes, proteins and cells through the vascular wall into the inflamed tissue. The main mechanism of exudation is an increase in the permeability of the vascular wall caused by the action of a number of pathogenetic factors. These include: destruction of the vascular wall during alteration; the rounding of endothelial cells and the formation of folding of the plasma membrane of endotheliocytes when the cytoskeleton is shortened; "displacement" of endothelial cells by leukocytes. Increased permeability in the first, early, short-term (5–30 min) phase is mediated by the action of biogenic amines and acetylcholine on postcapillary venules. In the later phase (1–7 days), increased permeability is mediated by the action of polypeptide and lipid mediators of unflammation on venules and capillaries. Microcirculation disorders and increased vascular permeability not only cause exudation, but also underlie leukocyte infiltration of the inflammatory focus, which sometimes reaches 50% of the daily production of phagocytes. The accumulation of neutrophils in the area of inflammation

reaches its peak 2–4 hours after its onset. In the blood, leukocytes are in an unactivated state. Their activation occurs in the center of inflammation, where they participate in phagocytosis. Neutrophils have the ability to absorb pathogenic microorganisms, as well as digest dead tissues, support the cascade of the inflammatory and reparative process. If neutrophils die during phagocytosis, macrophages remain, resorb the products of cell decay and intercellular substance, clearing the field for regeneration. This process is implemented with the help of such lysosomal enzymes as collagenase and elastase. A moving equilibrium is established between macrophages and fibroblasts - the main producers of collagen. Macrophages play an important role in the connection between exudative and proliferative phases of inflammation. Proliferation is the process of reproduction of connective tissue cells. The proliferative phase of inflammation ensures reproduction of the tissue structure, including all elements of the organ-tissue functional complex. Macrophages stimulate the proliferation of fibroblasts through the secretion of a number of BARs (cytokinins and growth factors). Fibroblasts ensure the formation of the main elements of the stroma during proliferation. At the same time, vascular neoplasia occurs. Strands of cells formed from the endothelium are separated from the capillaries. Later, a lumen of newly formed capillaries appears in these strands [1, 2].

Inflammation is classified according to the severity of the main local process (alterative, exudative and proliferative); body reactivity (normergic, hypoergic and hyperergic); type of exudate (serous, purulent, hemorrhagic, fibrinous, mixed); course (acute, subacute, chronic). The main physicochemical changes in the center of inflammation are hyperosmia, hyperonkyia, acidosis. Acidosis causes edema of connective tissue, increases exudation and local swelling. An increase in osmotic pressure increases exudation. Acidosis and increased osmotic pressure create conditions for the appearance of swelling (tumor) in the focus of inflammation. Redness (rubor) occurs as a result of the expansion of blood vessels, an increase in the flow of arterial blood containing bright red oxyhemoglobin, and the opening of capillaries that did not function before. An increase in local temperature (calor) can be explained by the influx of warmer arterial blood into the tissues and increased metabolism. Pain (dolor) occurs

as a result of irritation of sensitive nerve endings by various BARs — pain mediators (bradykinin, histamine, hypooxidized metabolic products, e.g. lactic acid), as well as as a result of tissue tension during swelling, which causes compression of sensitive nerve endings. A pronounced inflammatory process accompanied by changes in metabolism, blood circulation, innervation in tissues, as a rule, is manifested by a violation of the function of an organ or system (functio laesa). Along with local signs of inflammation in the body, general changes occur. A typical common feature of most inflammatory processes is an increase in the number of leukocytes per unit volume of peripheral blood (leukocytosis) and a change in the leukocyte formula. Quite often, inflammation is accompanied by fever. It develops under the influence of pyrogens produced by neutrophil leukocytes. During inflammation, the ratio of protein fractions of blood changes: the level of albumins decreases and the level of globulins increases. As a result of changes in the composition of protein fractions of blood plasma and a decrease in the charge of erythrocytes, the sedimentation rate of erythrocytes increases [1].

Inflammation is not only a protective reaction of the body, but also the most widespread pathological process, which is the basis of most (more than 70%) human diseases. Inflammation is the main pathogenetic component of many diseases of various etiology and one of the most important problems of general pathology and clinic. There is no branch of medicine that is not related to the prevention, diagnosis and treatment of the inflammatory process.

Pharmacological correction of inflammation, as before, remains a completely unsolved and urgent problem of modern medicine. This is due to the wide variety of inflammatory syndromes, the complexity of the pathogenetic mechanisms of the formation of inflammation, the not always sufficient effectiveness and safety of drugs used to correct inflammatory diseases.

1.2. General approaches to inflammatory diseases treatment

Glucocorticoid hormones, non-steroidal anti-inflammatory drugs (NSAIDs), a group of small immunosuppressants (heparin, chloroquine, D-penicillamine, drugs of gold, etc.), some enzyme drugs (vobenzym, etc.) have an anti-inflammatory effect and

are used to treat inflammatory diseases; astringent drugs (ethyl alcohol, etc.) have a local effect [2, 3].

NSAIDs are one of the most popular groups of drugs used in the treatment of inflammation. This is explained by the unique combination of their pharmacological features, which allows us to consider NSAIDs as one of the most important symptomatic and pathogenetic drugs. They are "first-line" drugs for the treatment of inflammatory diseases of the musculoskeletal system, and are also used in the complex therapy of neuralgia, prostatitis, adnexitis, cystitis, infectious and inflammatory diseases of the respiratory organs, etc. These drugs are taken by every seventh patient suffering from rheumatological diseases, and every fifth patient with other pathological conditions associated with pain, inflammation and fever. According to WHO, more than thirty million people in the world use NSAIDs every day [4, 5].

Analyzing the literature data on the pharmacological properties of modern NSAIDs, it should be emphasized that, despite the high clinical effectiveness, the use of NSAIDs has certain limitations, which can be explained by serious complications associated with their mechanism of action. Even short-term use of these drugs in small doses can lead to the development of side effects, which occur in approximately 25% of cases, and in 5% of patients are life-threatening [5, 6, 7, 8].

The main anti-inflammatory effect of NSAIDs is related to the blockade of the cyclooxygenase enzyme (COX-1, COX-2), which is actively synthesized in the center of inflammation, and is responsible for the synthesis of prostaglandins (PG), which are mediators of inflammation and pain.

Unfortunately, the positive effect of NSAIDs is accompanied by a large number of side effects, which significantly limits the possibility of their use. One of the most frequent complications of NSAIDs is damage to the gastrointestinal tract. When taking NSAIDs, inhibition of COX-1 activity leads to the development of erosion of the mucous membrane or its ulceration [9]. In 80% of patients, asymptomatic lesions of the gastrointestinal tract mucosa are detected several weeks after the start of NSAIDs treatment [4, 9, 10].

In 40-60% of patients who take NSAIDs for a long time, erosive ulcers in the gastroduodenal region are determined during endoscopy. Approximately 10-20% of patients receiving NSAIDs report dyspeptic disorders. In most cases, NSAID gastropathy develops during the first three months of treatment [9, 10].

The ulcerogenic activity of NSAIDs is caused by inhibition of the synthesis of PGE2 and prostacyclin in the gastric mucosa. Both tissue messengers perform protective, gastroprotective functions, stimulate the production of mucus, which forms a protective mucous barrier, inhibit the secretion of hydrochloric acid and improve tissue blood supply due to the expansion of blood vessels and improvement of microcirculation [4].

NSAIDs often cause ulcers of the small intestine. Even short-term intake (2 weeks) of diclofenac sodium in 68-75% of volunteers causes various damage to the small intestine: petechiae, erythema, violation of the integrity of the mucous membrane, the appearance of blood in the intestinal lumen [5]. Apoptosis of epithelial cells of the mucous membrane of the stomach, caused by indomethacin, is mediated by the development of microcirculatory disorders and thrombosis of intestinal vessels. Side effects from the gastrointestinal tract (GIT) cannot be avoided using suppositories or injectable forms of drugs. NSAIDs (indomethacin and diclofenac sodium), suppressing the synthesis of PG, can cause renal failure, arterial hypertension, interstitial nephritis and even necrosis of the papillae in the kidneys [6, 11].

Blockade of the synthesis of PGE2 and prostacyclin in the kidneys leads to narrowing of blood vessels, deterioration of renal blood flow, ischemic changes in the kidneys, reduction of glomerular filtration and diuresis volume, therefore causes edema, hypernatremia, hyperkalemia, elevated serum creatinine and uric acid levels, and increased blood pressure. Hyperuricemia (associated with suppression of urate secretion in the distal tubules of the kidneys) can cause an acute attack of gout [6].

The current large assortment of anti-inflammatory drugs does not solve the problem of successful treatment of inflammatory diseases and their relapses, the frequency of which after drug withdrawal can be almost 100% of cases [12, 13, 14]. In addition, long-term and simultaneous use of these drugs contributes to an increase

in the frequency of complications of anti-inflammatory pharmacotherapy. Therefore, the search for anti-inflammatory drugs for the treatment of inflammatory diseases remains relevant today. Research on new anti-inflammatory drugs is conducted taking into account the pathogenesis of inflammatory diseases [10].

That is why, despite the diverse range of anti-inflammatory drugs, new complex treatment regimens and drugs with unconventional mechanisms of action and minimal side effects are constantly being sought to correct inflammation. One of the promising directions for the creation of safe and effective anti-inflammatory agents is the use of herbal drugs.

1.3. The role and place of plant origin drugs in inflammatory diseases treatment

The listed side effects of NSAIDs and the need for their widespread use necessitate the search for safer anti-inflammatory agents, a promising source of which are drugs created on the basis of plant raw materials. Their therapeutic value is proven by a thousand-year history of use and is scientifically substantiated by the results of numerous preclinical and clinical studies. The pharmacological activity of natural compounds is due to their low toxicity, the ability to have a complex effect on the body and rarely cause serious side reactions. This allows for long-term treatment of chronic diseases. The undeniable advantage of herbal preparations is the availability of raw materials and the economical way of obtaining the medicine.

In recent years, interest in herbal drugs has increased. They do not have the disadvantages inherent in synthetic drugs, have a milder physiological effect, do not suppress the body's immune system. Science knows almost 500,000 species of plants, of which only about 290 are described as medicinal. At the beginning of the 20th century, medicinal plants accounted for up to 80% of all existing drugs, but then synthetic, hormonal drugs, antibiotics significantly suppressed them. However, despite the success in the creation of synthetic drugs, herbal medicines occupy an important place in modern medicine. Medicinal plants are characterized by a wide variety of chemical composition and contain dozens of pharmacologically active substances. Today, many

chronic diseases are successfully treated with the help of medicinal plants, therefore phytotherapy is one of the most important sections of medicine [15].

All plants with anti-inflammatory properties can be divided into three groups depending on the content of one or another active substance in them.

The first group is plants that contain salicylates. Acetylsalicylic acid, the progenitor of anti-inflammatory agents, is obtained from willow bark. Antipyretic properties of willow were known even before our era, and the main active substance salicin was isolated from its bark in 1828. Later, the well-known salicylic acid and then acetylsalicylic acid were obtained from this alkaloid. Salicylates contain the following plants: yarrow, peony (root), raspberry (leaf), white willow (bark), black poplar (buds) and others. In the acute period of the inflammatory process, it is advisable to prescribe preparations of medicinal plants containing salicylic compounds.Найбільш вираженою протизапальной активністю володіють глікозиди саліцин, кверцетин, саліцилова та гліциризинова кислоти, деякі флавоноїди, вітаміни-антиоксиданти та ефірні олії [15].

The second group of plants with anti-inflammatory properties contains so-called phytosterols, di- and triterpenoids and other substances with a steroid structure. Their structure and, accordingly, pharmacological properties are close to the action of glucocorticosteroids. Phytoestrogens bind to estrogen receptors of cartilage cells and prevent their destruction. The largest amount of phytosterols is found in licorice. Currant leaf, bittersweet nightshade, yellow cypress, marsh bog, daurian rhododendron, mountain saltwort, poison ivy, chinese angelica or angelica, alfalfa seed and others also contain phytosterols. [16].

In the treatment of osteoarthritis, herbal preparations rich in phytoestrogens are most often used. Women suffer from osteoarthritis more often than men, because estrogens play a leading role in the development of this disease. Historically, plants such as licorice root, chinese angelica, and alfalfa have been used in the treatment of osteoarthritis. [15, 16].

The third group of anti-inflammatory plants realizes an anti-inflammatory effect only when applied to an open inflamed wound or mucous membranes. These plants

contain tannins and gallic acid, have an astringent effect, which provides an anti-inflammatory effect. When the BAS of these plants gets on the wound surface or mucous membrane, surface proteins are bound, as a result of which a dense film of albuminates is formed, which protects tissues from irritation and promotes reparation. This leads to the narrowing of blood vessels and a decrease in their permeability and reduces exudation. The secretion of glands also decreases and the sensitivity of nerve endings decreases. This is how the anti-inflammatory effect of such plants as badan, oak, tannin, alder, sage, chamomile and others is manifested [16].

Medicinal plants that have been used in folk medicine for the treatment of inflammatory diseases since ancient times include large burdock.

1.4. Justification of the feasibility of studying the anti-inflammatory properties of a thick extract of burdock leaves

Large burdock (Arctium lappa L.) belongs to the Compositae family [15, 16, 17]. It is widespread in the temperate zones of Eurasia and North America. The leaves are very large, can reach 40 cm in length. In folk medicine, burdock is widely used for inflammatory diseases of the skin, respiratory tract, liver, pancreas, joints, kidneys, and gastrointestinal tract. In many countries, burdock is an official medicinal plant and is used in the treatment of many diseases.

Burdock is an alternative source of phenolic hydroxycinnamic acids, organic acids and flavolignans (diarctigenin, arctigenin, dimethyltraxylagenin, dibenzylbuterolactone) [18, 19]. Both roots and leaves of burdock are used as medicinal raw materials. Burdock leaves contain ascorbic acid, carotene, rutin, hyperoside, essential oil, mucilage, tannins. The following substances were found in burdock leaves: a high concentration of vitamin C (200-250 mg per 100 g) and B vitamins (about 70% of the daily dose); minerals - zinc, selenium, manganese, iron; inulin; essential oils; tannins; organic acids [20, 21]. These elements give the plant anti-inflammatory, diuretic and wound-healing properties [22, 23, 24, 25].

Thanks to the valuable elements, the medicinal properties of burdock leaves are used to combat many diseases. An infusion of greens, used as an external remedy,

relieves inflammation and acne on the face. It also reduces the activity of the sebaceous glands and eliminates greasy shine. Daily use alleviates the symptoms of psoriasis and eczema due to its anti-inflammatory and wound-healing effect [26, 27]. Drinks made from burdock leaves stimulate the work of the liver and kidneys, which accelerates the removal of harmful substances. Alcohol-free infusions of burdock are used for pancreatitis, hepatitis and cholecystitis. A compress made from mashed leaves is effective in the treatment of joints. Course intake of tea is effective for gout [28, 29, 30]. The use of fennel leaves eases the course of urolithiasis and eliminates inflammation of the urinary tract. Taking decoctions helps to get rid of constipation, because they have a mild laxative effect. During colds and SARS, the drinks help reduce the temperature and have a diaphoretic effect. In case of inflammation of the nasopharynx and oral cavity, it is necessary to regularly rinse with infusions of burdock leaves. It improves the functioning of the endocrine system and stabilizes the hormonal background. In case of sunburn, it is recommended to apply a mixture of burdock leaves and egg whites to the affected area of the skin. Vitamin drinks made from burdock have a tonic effect and enrich the body with necessary substances. Burdock leaves are used to prevent infertility, treat inflammatory diseases of the mammary gland, uterine fibroids. In addition, with the constant use of medicinal drinks, the menstrual cycle is normalized, and pain during its flow is reduced [31, 32, 33].

On the basis of the leaves, you can prepare decoctions, infusions for external and internal use. Burdock leaves are used for the following diseases: warts; inflammatory processes of the oral cavity; skin rash, boils, ulcers; joint and spinal pain, relief of inflammation after insect bites; prevention, treatment of hair loss; swelling of the legs. [34] Infusions or decoctions stimulate metabolic processes, increase the outflow of urine and bile, destroy pathogenic flora, normalize the work of the pancreas, increase the body's ability to resist the formation of tumors, activate the work of mammary and sweat glands [32, 33, 35, 36]. There is information about the anti-allergic properties of burdock leaves. Leaf juice is used in the treatment of hepatitis and other liver diseases [37, 38].

For external use, the leaves are used for the following diseases: warts;

inflammatory processes of the oral cavity; skin rash, boils, ulcers; articular and spinal pain, relief of inflammation after insect bites; prevention, treatment of hair loss; swelling of the legs [39, 40, 41]. There is information about the culture's ability to effectively eliminate allergic reactions. The juice of young leaves is used in the treatment of hepatitis and liver diseases. Juicy leaves are used for burns, wounds, sprained ligaments. It is young shoots that have powerful wound-healing and antimicrobial activity [42, 43, 44]. In case of rheumatoid arthritis, they are applied at night with the lower side to the diseased joint, bandaged. After rinsing with boiling water, they are used for headaches. The decoction is used to wash the throat with sore throat. Decoctions and infusions of burdock are used in the treatment of infertility, uterine fibroids, mastopathy, and for the prevention of miscarriages. Regular use of a decoction of shoots helps to reduce blood loss during heavy menstrual bleeding or uterine bleeding. In the presence of fibroids, herpes, cystitis, a decoction of burdock is taken [45].

Burdock leaves are used in the treatment of prostatitis. Due to the presence of inulin in the composition of the culture, the lymph flow increases, due to which the inflammatory processes in the prostate gland are removed, the urination process is normalized, and metabolic processes are improved [46, 49].

The use of burdock in folk medicine is quite wide, such as cystitis, colitis, laryngitis, pancreatitis, stomatitis, hepatitis, tonsillitis, gastritis, hepatitis, osteochondrosis, alcohol poisoning, diabetes, urolithiasis, constipation, hemorrhoids, psoriasis, furunculosis , burns, eczema, acne, seborrheic dermatitis, poorly healing wounds [47, 48].

Burdock juice obtained from the leaves is an excellent medicine. The juice, like other burdock preparations, has a diuretic, choleretic, diaphoretic, antibacterial and anti-inflammatory effect [22]. In addition, it has pronounced anti-rheumatic, anti-diabetic and anti-allergic activity, improves liver and kidney function, metabolism and protein assimilation, normalizes blood composition. Burdock juice is rubbed into the scalp to strengthen hair.

Despite the fact that burdock drugs are widely used in traditional medicine, there is not enough reliable data on the results of their experimental and clinical studies.

Conclusions for chapter 1

Thus, on the basis of the above literature data, it is relevant to conduct an in-depth study of the anti-inflammatory activity of a thick extract of burdock leaves. This will allow to expand the range of domestic anti-inflammatory drugs and will contribute to the optimization of anti-inflammatory therapy.

CHAPTER 2
MATERIALS AND METHODS

The study used a thick extract of large burdock leaves, obtained and studied at the Department of Botany of the National Academy of Sciences under the guidance of Prof. Chvorost O.P. [49]. Phytochemical composition of burdock leaves extract is given in table 2.1.

Table 2.1

Phytochemical composition of large burdock leaf thick extract

[50]

Pharmacologically active substance	Number, %
Inulin	5,14
Hydroxycinnamic acids	2,12
Flavonoids	3,21
Tanning substances	1,07
Ascorbic acid	0,065
Macro- and microelements	18,35
Amino acids	4,63

The anti-inflammatory properties of a thick extract of burdock leaves were studied on models of acute aseptic inflammation - carrageenan and zymosan edema, on the model of acetic acid ulcers and the model of cotton wool granuloma in rats. Experimental models were reproduced in accordance with the methodological recommendations of State expert center (SEC) of the Ministry of Health of Ukraine for the preclinical study of medicinal products [51].

Reference NSAIDs diclofenac sodium and indomethacin, as well as a plant origin drug with proven anti-inflammatory properties - quercetin, were chosen as comparison drugs.

When conducting research on the pharmacological activity of potential anti-inflammatory agents, one of the adequate and informative criteria for their activity is the

antiexudative effect [51]. Therefore, at the first stage of the work, the antiexudative effect of a thick extract of burdock leaves was studied on models of acute aseptic inflammation.

Anti-inflammatory drugs with different mechanisms of action have an effect on individual pathophysiological and biochemical links of inflammation, or on several at the same time. Considering the fact that inflammation caused by different phlogogenic agents differs in the features of its development and the factors involved in its genesis, it was reasonable to investigate the antiexudative properties of a thick extract of burdock roots in a wide range of doses in models of acute inflammation induced by different phlogogenic agents - carrageenin and zymosan NSAIDs with a pronounced anti-inflammatory effect - diclofenac sodium and a herbal preparation with proven anti-inflammatory activity - quercetin [52] were chosen as comparison drugs. Also, the choice of quercetin can be explained by the fact that, as is known, its mechanism of action is associated with inhibition of 5-lipoxygenase and blocking of leukotriene synthesis. In this and subsequent studies, we will use sodium diclofenac under the Voltaren trade mark, gastro-resistant tablets of 25 mg, produced by the Novartis company, and quercetin granules of Borshchagivskyi chemical and pharmaceutical plant (Ukraine)

In order to determine the average effective dose of a thick extract of burdock leaves when studying its antiexudative activity, it was administered intragastrically in doses of 25; 50 and 75 mg/kg. Diclofenac sodium was administered intragastrically at a dose of 8 mg/kg, which is the ED50 dose for antiexudative activity [51]. Quercetin was administered intragastrically in a conditionally effective dose, which, according to the literature, is 50 mg/kg. Control animals were injected with an equivalent amount of solvent. The drugs were administered prophylactically for 4 days before the reproduction of the model pathology, the last time - 1 hour before the induction of inflammation. Solutions or suspensions of the studied substances were administered in all experiments at the rate of 1 ml per 100 g of animal weight.

Acute aseptic inflammation was reproduced by the introduction of 1% carrageenan solution and 2% zymosan solution [51]. Phlogogenic agents were

administered to rats subplantarly in a volume of 0.1 ml per animal 1 hour after the last administration of the studied drugs.

Measurement of paw edema in rats on two models of edema was performed using a mechanical oncometer according to A.S. Zakharevsky in dynamics:

- after 1, 2, 3, 4, 5 and 6 hours after carrageenan administration;
- after 1, 2, 3, 4 hours after zymosan administration.

The antiexudative activity of the studied drugs in acute exudative inflammation was determined by the ability to reduce the development of edema in comparison with the group of control pathology, was calculated according to the following formula and expressed as a percentage.

$$A = 100\% - \frac{(M_o - M_з) \times 100}{M_o^к - M_з^к}, \text{ де}$$

A – antiexudative activity, %;

M_o – the volume of the swollen paw in the experiment (in treated animals);

$M_з$ – the volume of a healthy paw in the experiment;

$M_o^к$ – the volume of the swollen paw in the control (in untreated animals);

$M_з^к$ – the volume of a healthy paw in control.

In studies of the anti-exudative activity of the extract of burdock leaves, its conditionally effective dose was determined, which is 25 mg/kg. It was used in further studies.

The second stage of studying the anti-inflammatory activity of the studied extract was to determine its effect on the development and course of inflammation with a predominance of alterative processes.

In the alterative stage of inflammation, a variety of biochemical and morphological changes occur, which are manifested in the form of dystrophy and necrosis and are aimed at the inclusion of integral regulatory systems of the entire body in the inflammatory process [1].

Research on the anti-alterative activity of burdock leaf extract was carried out on the model of acetic acid ulcers in rats in accordance with the methodological

recommendations of SEC of the Ministry of Health of Ukraine for the preclinical study of medicinal products [51]. Diclofenac sodium and quercetin were selected as reference drugs. Experiments were carried out on purebred white rats weighing 170-200 g.

Necrotic ulcers were caused by injecting experimental animals subcutaneously with 0.5 ml of a 9% solution of acetic acid and at the same time intraperitoneally with a 6% solution of dextran at a dose of 300 mg/kg. The latter was administered in order to sensitize the animal's body and enhance the necrotic reaction. The studied drugs were administered in a therapeutic regimen for 25 days once a day: burdock leaf extract - in a conditionally effective dose of 25 mg/kg, sodium diclofenac - in a dose of 8 mg/kg, quercetin - in a dose of 50 mg/kg. Measurement of the area of ulcers was carried out by the planimetric method in dynamics on the 7th, 12th, 20th and 25th day of the study. To determine the antialterative and reparative activity of the studied drugs, we used the following indicators.:

1. Wound area, мм^2;
2. Wound healing rate (%), calculated by the formula:

$$V = 100 \times \frac{S_o - S_t}{S_o}, \text{ де}$$

S_o – maximal wound area, мм^2;

S_t – wound area on the day of measurement, мм^2.

3. Percentage of animals with wounds that scarred.

It is known that excessive proliferation leads to significant violations of the functional state of organs and systems, especially the musculoskeletal system. Therefore, we conducted a study of the antiproliferative properties of burdock leaf extract.

The well-known NSAID indomethacin was chosen as the comparison drug, as it outperforms other NSAID drugs and quercetin in terms of antiproliferative activity [52]. We used indomethacin under the trade mark "Indomethacin Sopharma" manufactured by "Sopharma" (Bulgaria) enteric-coated tablets, 25 мг.

Studies on the antiproliferative effect of a thick extract of burdock leaves were conducted on a model of cotton wool granuloma in rats. Experiments were carried out on purebred white rats weighing 180-210 g.

The model pathology was reproduced in accordance with the methodological recommendations of SEC of the Ministry of Health of Ukraine for the preclinical study of medicinal products [50]. In rats, under light ether anesthesia, a skin area was depilated on the back, and in aseptic conditions, a longitudinal incision of the skin and subcutaneous tissue with a length of 1.5 cm was made with scissors, a cavity was formed, where a sterile cotton ball weighing 15-20 mg was placed, after which a 1- 2 stitches. At the end of the 8th day of the experiment, the implanted ball with the granulation tissue formed around it was removed, dried to a constant mass at a temperature of 55-60°C. The mass of the formed granulation-fibrous tissue was determined by the difference between the mass of the dried granuloma and the implanted cotton ball.

Burdock extract was administered intragastrically in a conditionally therapeutic dose of 3 mg/kg, indomethacin in a dose of ED_{50}, which is 10 mg/kg, and quercetin in a dose of 50 mg/kg, in a therapeutic regimen for 7 days from the moment of implantation of a sterile cotton ball.

The antiproliferative activity of the studied substances was determined by their ability to suppress the formation of granulation tissue in comparison with the control and was expressed as a percentage (%).

Pharmacological studies were carried out on 104 standardized rats, grown in the vivarium nursery of the central research laboratory of NUPh.

Student's t-test (for pairwise comparisons) or one-way analysis of variance ANOVA was used to find out intergroup differences in the case of normal distribution of sample data. In the absence of a normal distribution, the Mann-Whitney U-test was used.

When working with animals, the requirements of the Law of Ukraine "On the Protection of Animals from Cruelty Treatment" (Ukraine, 2006), coordinated with the "European Convention on the Protection of Vertebrate Animals Used for Experimental

and Other Scientific Purposes" (Strasbourg, 5 1986), the Order of the Ministry of Education and Science, Youth and Sports of Ukraine dated 01.03.2012 No. 249 "On Approval of the Procedure for Research and Experiments on Animals by Scientific Institutions".

Conclusions for chapter 2

Thus, the test system and the object of research are determined. In accordance with the purpose of the work, an adequate set of methods was chosen, allowing to maximally assess the presence or absence of anti-inflammatory properties in the object of research - a thick extract of large burdock leaves. Relevant methods of statistical analysis of the results are proposed.

CHAPTER 3
STUDY RESULTS

It is known that in the preclinical study of the pharmacological activity of potential anti-inflammatory agents, one of the adequate and informative criteria for their activity is the antiexudative effect. Also taking into account the fact that exudation is the initial stage of any inflammatory process, in addition, in order to determine the average effective dose, it was appropriate to begin the study of the anti-inflammatory properties of the thick extract of large burdock by determining its anti-exudative activity on models of acute exudative inflammation.

To study the anti-edematous effect of the thick extract of burdock roots, we chose models of carrageenan and zymosan edema. The choice of models is determined by their informativeness and ease of reproduction. The diversity of the mechanism of the development of acute exudative inflammation in these models of edema will allow us to more thoroughly study the features of the antiexudative effect of the studied drugs, since prostaglandins (PG) are mainly involved in the development of carrageenan edema, and leukotrienes (LT) are mainly involved in the development of zymosan inflammation. Quercetin, a plant-derived drug with anti-exudative activity proven in previous studies, and diclofenac sodium, which is a reference anti-inflammatory agent, were chosen as comparison drugs [2, 3].

The studied objects were administered intragastrically in a prophylactic mode for five days before the reproduction of the model pathology. Burdock leaf extract was administered in doses of 25; 50 and 75 mg/kg, which were chosen according to the methodological recommendations of the pre-clinical study of drugs, quercetin - in a conditionally effective dose of 50 mg/kg, diclofenac sodium in an ED_{50} dose of 8 mg/kg [51] . Acute aseptic inflammation was reproduced by subplantar administration of 1% carrageenan solution and 2% zymosan solution in a volume of 0.1 ml per animal 1 hour after the last administration of the studied substances.

The amount of paw edema in rats with acute exudative inflammation was measured using a mechanical oncometer according to A.S. Zakharevsky in the dynamics of

carrageenan edema - after 1, 2, 3, 4, 5 and 6 hours, with zymosan edema - after 1, 2, 3 and 4 hours after the introduction of the corresponding phlogogenic agent. The antiexudative activity of the studied substances was determined by the ability to reduce the development of edema in comparison with the group of control pathology, it was calculated and expressed as a percentage.

3.1. Study of the antiexudative effect of a thick extract of burdock leaves on the model of carrageenan edema in rats

The introduction of a carrageenan solution led to swelling of the hind limbs in experimental animals. Thus, in rats from the control pathology group, the paw volume increased 1.2 times after 1 hour, 1.6 times after 2 hours, 1.6 times after 3 hours, and 1.8 times after 4 hours. once, after 5 hours - 1.7 times, after 6 hours - 1.5 times. The maximum swelling was observed during 3, 4 and 5 hours and remained until the end of the study (tabl. 3.1).

The introduction of the studied substances led to a significant reduction in the swelling of the limbs of the experimental animals. At 1 hour of the study, only the extract of burdock leaves at a dose of 25 mg/kg (28.5%) showed reliable antiexudative activity, the activity of diclofenac sodium was 27.7%, but the changes in the volume of rat paws were not reliable. At the end of 2 hours, diclofenac sodium showed the greatest antiexudative activity (71.4%), the effect of burdock leaf extracts in doses of 25, 50, and 75 mg/kg was inferior to that of diclofenac (43.3%, 27.3%, and 39.4%, respectively) . Quercetin did not show a reliable anti-exudative effect during the first 2 hours of the study.

At the end of the third hour, burdock extract in all doses and both reference drugs showed a reliable anti-edematous effect. Diclofenac sodium was the most active, its anti-exudative activity was 79.2%. It was slightly inferior to burdock leaf extract in doses of 25 and 50 mg/kg, the antiexudative effect was 57.8% and 45.9%, respectively. The anti-edema effect of burdock leaf extract at a dose of 75 mg/kg was 38.2%. Quercetin showed less anti-exudative activity – 27.9%.

Table 3.1

Antiexudative activity of burdock leaf extract on the carrageenan edema model in rats (n = 5)

Substances	Paw volume (in conventional units)/anti-exudative activity (in %) during							
	initial	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours	average
Control pathology	48.1±1.4	59.6±3.5	67,9±2,2	78.2±2.1	84.5±1.4	81.0±3.0	73.4±1.9	-
Burdock leaf extract, 25 mg/kg	46.7±1.2	54.9±1.3* 28.5	57.9±1.6* 43.3	59.4±3.0* 57,8	55.3±3.5* 76.5	57.5±2.8* 67.2	53.5±2.5* 71.1	57.4
Burdock leaf extract, 50 mg/kg	46.4±2.1	55.2±3.2 23.4	60.8±2.0* 27.3	62.9±2.1* 45.9	65.6±1.9*/** 47.3	63.0±1.4* 49.5	64.5±2.6*/** 29.0	37.1
Burdock leaf extract, 75 mg/kg	46.2±1.3	54.1±1.7 31.3	58.2±2.1* 39.4	64.8±2.6* 38.2	60.9±3.5* 59.6	63,2±2,0* 48,3	62.1±2.4* 37.6	42.4
Quercetin, 50 mg/kg	49.9±2.0	59.2±4.0 19.4	64.9±2.1 24.2	71.6±1.7* 27.9	75.6±2.4* 29.5	74,1±1,9* 26,3	69.8±1.4 21.5	24.8
Diclofenac sodium, 8 mg/kg	48.5±1.5	56.8±3.1 27.7	54.2±2.9* 71.4	54.8±3.2* 79.2	52.7±4.2* 88.4	55,7±2,2* 78,0	58.8±3.7* 59.1	67.3

Note. Statistically significant differences ($p \leq 0.05$): * - to control pathology.

During the next hour, diclofenac sodium was the most active (88.4%), the anti-edema effect of burdock leaf extract at a dose of 25 mg/kg was 76.5%, the effect of burdock leaf extract at a dose of 50 mg/kg was 49.9%, in dose of 75 mg/kg – 59.6% Quercetin showed the least activity (29.5%).

A similar picture was observed at five o'clock. Diclofenac sodium showed the maximum activity (78%), burdock leaf extract at a dose of 25 mg/kg was somewhat inferior to diclofenac sodium, its activity was 67.2%. Burdock leaf extract in doses of 50 and 75 mg/kg at this time showed almost the same effect - 49.5% and 48.3%, respectively. Quercetin was the least active, its anti-edema effect was 26.3%.

At the end of the study, burdock leaf extract at a dose of 25 mg/kg was the most active (71.1%), other drugs were inferior to it in terms of anti-edema effect. The effect of diclofenac sodium was 59.1%, the effect of burdock leaf extracts in doses of 50 and 75 mg/kg was 29% and 37.6%, respectively. Quercetin did not show reliable anti-exudative activity.

According to the average anti-exudative activity, the investigated substances can be placed in the following series: diclofenac sodium (67.3%) > burdock leaf extract, 25 mg/kg (57.4%) > burdock leaf extract, 75 mg/kg (42.4%) ≥ burdock leaf extract, 50 mg/kg (37, 1%) > quercetin (24.8%).

Therefore, in this model of inflammation, the extract of burdock leaves at a dose of 25 mg/kg showed the greatest anti-edematous effect.

3.2. Study of the antiexudative effect of burdock leaves extract on the model of zymosan edema in rats

It is known that the metabolism of arachidonic acid can occur not only by the oxygenic (cyclooxygenase) but also by the anoxic (5-lipoxygenase) pathway, which leads to the formation of leukotrienes [1, 3]. To determine the effect of burdock root extract on the exudation phase of the inflammatory process in rats with zymosan edema, the leading role in the development of which belongs to leukotrienes, as well as to confirm the choice of a conditionally effective dose of

the studied extract, it was advisable to investigate the anti-edematous effect of the above-mentioned drugs on the model of zymosan edema in rats . Quercetin was chosen as a comparison drug, together with sodium diclofenac, as a drug that has the ability to inhibit the 5-lipoxygenase pathway of arachidonic acid transformation [52]. The results of the study are shown in the table. 3.2.

The introduction of a phlogogenic agent caused swelling and an increase in the volume of the limbs of experimental animals by an average of 1.2-1.7 times (табл. 3.2).

Prophylactic administration of drugs contributed to a reliable reduction in the volume of rats, that is, all studied substances showed an anti-inflammatory effect to varying degrees. In the first and second hours of the experiment, only the extract of burdock leaves at a dose of 25 mg/kg showed a reliable anti-exudative effect, which was 27% and 37.4%, respectively. Other drugs also showed an anti-edematous effect, but it was unreliable. That is, it is possible to claim only about the tendency to anti-edematous action.

At the third hour, all substances, except the extract of burdock leaves at a dose of 50 mg/kg, showed a reliable anti-edematous effect. Burdock leaf extract maximally reduced paw swelling in doses of 25 mg/kg (49.9%) and 50 mg/kg (45.8%).

Quercetin and diclofenac sodium acted almost equally, their antiexudative activity was within 41.5%. The least active was the burdock leaf extract at a dose of 50 mg/kg (32.6%).

At the end of the fourth hour, quercetin (45.9%) and burdock leaf extract at a dose of 25 mg/kg (42.1%) most actively reduced the swelling of the limbs of experimental animals. Burdock leaf extract at a dose of 75 mg/kg (33.6%) and diclofenac sodium (30.8%) were less active. In the extract of burdock leaves at a dose of 50 mg/kg, only a tendency to anti-edema effect was observed.

Table 3.2

Antiexudative activity of burdock leaf extract

on the model of zymosan edema in rats (n = 5)

Substances	Paw volume (in conventional units)/anti-exudative activity (in %) during					
	initial	1 hour	2 hours	3 hours	4 hours	average
Control pathology	46.3±1.0	56.0±1.6	61.5±2.0	69.9±1.5	78.2±2.8	-
Burdock leaf extract, 25 mg/kg	44.2±2.1	51.3±1.2* 27.0	53.7±1.8* 37.4	56.3±3.7* 49.9	62.0±3.7* 42.1	39.1
Burdock leaf extract, 50 mg/kg	46.9±1.1	54.2±2.9 24.7	58.6±1.5 23.0	62.8±2.2* 32.6	64.7±1,8* 42.0	30.6
Burdock leaf extract, 75 mg/kg	49.7±1.1	56.9±2.6 25.8	58.8±3.2 40.1	62.5±1.9* 45.8	70.1±1.2* 33.6	36.3
Quercetin, 50 mg/kg	48.8±1.7	56.2±2.7 23.9	58.1±1.5 38.7	62.7±1.3* 41.1	65.4±3.1* 45.9	37.4
Diclofenac sodium, 8 mg/kg	47.0±2.0	54.0±4.2 28.1	56.7±1.9 36.2	60.8±2.0* 41.5	68.2±2.6* 30.8	34.2

Note. Statistically significant differences ($p \leq 0.05$): * - to control pathology.

According to the average active-exudative effect, the drugs are located in the next row: burdock leaf extract, 25 mg/kg (39.1%) ≥ quercetin (37.4%) = burdock leaf extract, 75 mg/kg (36.3%) ≥ diclofenac sodium (34.2%) ≥ burdock leaf extract , 25 mg/kg (30.6%).

Burdock leaf extract at a dose of 25 mg/kg showed the greatest anti-edematous activity.

The study of the antiexudative effect of large burdock extracts was carried out on models of carrageenan and zymosan edema in rats. The choice of models is due to their informativeness, since at each stage of the development of inflammation, other things being equal, a certain group (or groups) of mediators participating in the development of the exudative reaction is of primary importance. Yes, in the first 30-90 minutes. biogenic amines – serotonin and histamine are involved in the pathogenesis of acute inflammation. In the interval between 1.5-2.5 hours, the kinin system is activated (bradykinin, kallidin, complement fragments), and between 2.5-5.5 hours - leukotrienes, prostaglandins [51].

The diversity of the mechanism of development of acute exudative inflammation in selected models of edema, determination of the effect of a thick extract of burdock leaves on the course of models of acute aseptic inflammation made it possible to study the features of the mechanism of antiexudative action and to determine the conditionally effective dose of the extract, which is necessary for further research.

3.3. Study of the antialterative activity of burdock leaves extract on the model of acetic acid ulcers in rats

It is known that the anti-inflammatory effect consists of anti-alterative, anti-exudative and anti-proliferative components.

In previous studies, it was established that the thick extract of burdock has a moderate anti-exudative activity, and this makes it reasonable to further study its anti-

alterative and anti-proliferative activity. Conditionally effective dose of burdock leaf extract is 25 mg/kg.

Alteration is the first phase of the inflammatory process. It is she who starts the entire cascade of inflammation, causing destructive changes in the affected tissue. Therefore, suppression of inflammation at the stage of its initiation is an important component of the success of anti-inflammatory therapy.

The study of the antialterative activity of a thick extract of burdock leaves was carried out on the model of acetic acid skin ulcers in rats. Experiments were conducted on purebred white rats weighing 170-200 g. Diclofenac sodium and quercetin were selected as reference drugs.

The animals were divided into four groups: I – control pathology; II – rats injected with burdock leaf extract at a dose of 25 mg/kg; group III - rats administered diclofenac sodium at a dose of 8 mg/kg, and group IV - animals administered quercetin at a dose of 50 mg/kg.

The studied objects were administered in the treatment mode once a day for 25 days after the administration of the solution of acetic acid and dextran. Measurement of the area of ulcers was carried out by the planimetric method in dynamics on the 8th, 12th, 20th and 25th day of the study.

The obtained results are shown in the table.3.3-3.4.

It was established that during the first 6 days after the injection of acetic acid and dextran solutions into rats, the formation of an ulcer surface was observed (exclusion of necrotic tissue, purulent exudate was observed in some animals). On the 7th day, the area of the wound process was maximal, after which wound healing began, which lasted until the end of the study (25th day).

According to the results of the experiment, on the 7th day, none of the studied drugs showed a significant anti-alterative effect, since the average area of ulcers in the animals of the above-mentioned groups was not significantly different from the similar indicator in the group of animals with control pathology (table 3.3). This coincides with information about the pharmacodynamics of NSAIDs [3, 52].

In the animals of the control pathology group, spontaneous healing of ulcers occurred during 12-20 days of observation, the area of ulcers decreased by 12.4% on the 12th day, and by 25.6% on the 20th day. Wounds healed most intensively in the period from 20 to 25 days, the rate of wound healing was 48.6%. However, by the end of the experiment (on day 25), the wounds did not fully heal in any animal.

In the treated animals, activation of the granulation process began on the 12th day. During this period, in the group of animals that received quercetin and a thick extract of burdock leaves, the area of ulcers decreased to 244.2 and 241.3 mm2, respectively, and did not statistically differ from the indicator of the control pathology group, the rate of wound healing was equal to 17% and 13.1 % respectively. When diclofenac sodium was used on the 12th day, a wound healing rate of 22.8% was observed, and the area of ulcers in this group decreased to 206.3±10.9 mm^2, which was significantly different from the similar indicator in the control pathology group (table 3.3).

On the 20th day of the experiment, the rate of wound healing in all groups of treated animals increased significantly, it was 34.9% in the groups of animals treated with quercetin, 38.3% in rats treated with burdock leaf extract, 48.9% in the group of rats, treated with diclofenac sodium.

The average area of ulcers in the group of animals that received burdock leaf extract was 171.3±7.4 mm^2. In animals treated with sodium diclofenac, the average area of ulcers was 136.8±9.2 mm^2. The average area of ulcers in the group of animals injected with quercetin did not significantly differ from the similar indicator in the animals of the control pathology group and was equal to 191.6±12.0 mm^2.

At the end of the 25th day, the area of ulcers in all groups of animals treated with the studied drugs, except for those treated with quercetin, was significantly smaller compared to the control pathology group. The smallest average area of ulcers was recorded in animals treated with diclofenac sodium – 65.3 mm^2. In rats treated with burdock leaf extract, the average ulcer area was 87.3 mm^2. The average area of wounds in animals that were injected with quercetin was 128.7 mm^2 and was not

significantly different from the rate of spontaneous wound healing in animals of the control pathology group.

Table 3.3

Dynamics of changes in the area and speed of wound healing under the influence of a thick extract of burdock leaves on the model of acetic acid ulcers in rats (n=5)

Substances	7 day	12 day		20 day		25 day		Average V, %
	Wound area, mm^2	Wound area, mm^2	V, %	Wound area, mm^2	V, %	Wound area, mm^2	V, %	
Control pathology	284.7± 10.3	249.5± 8.2	12,4	211.9± 10.5	25.6	146.4± 10.1	48.6	28.9
Burdock leaf extract, 25 mg/kg	277.8± 11.2	241.3±12.9	13,1	171.3± 7.4*	38.3	87.3± 6.9*/**	68.6	40.0
Quercetin, 50 mg/kg	294.3± 14.1	244.2± 9.4#	17,0	191.6± 12.0#	34.9	128.7± 9.6#	56.3	36.1
Diclofenac sodium, 8 mg/kg	267.5± 12.6	206.3± 10.9*/**	22,8	136.8± 9.2*/**	48.9	65.3± 5.4*/**	75.6	49.1

Notes:

1. statistically significant differences ($p \leq 0.05$): * - to control pathology, ** - to quercetin, # - to diclofenac sodium;

2. V – speed of wound healing;

3. n – the number of animals in the group.

In terms of average reparative activity (23.8%), burdock leaf extract (21%) was inferior to sodium diclofenac (36%) and exceeded the effect of quercetin (7.9%) (table 3.4).

Table 3.4

Dynamics of the reparative activity of the thick extract burdock leaves on the model of acetic acid ulcers (%) (n=5)

Substances	12 day	20 day	25 day	Average activity	% animals with wounds that have healed
Control pathology	–	–	–	–	0
Burdock leaf extract, 25 mg/kg	3.3	19.2	40.4	21.0	40.0
Quercetin, 50 mg/kg	2.1	9.6	12.1	7.9	20.0#
Diclofenac sodium, 8 mg/kg	17.3	35.2	55.4	36.0	60.0*/**

Notes:

1. statistically significant differences ($p \leq 0.05$): * - to control pathology, ** - to quercetin, # - to diclofenac sodium;

2. n – the number of animals in the group.

In terms of average reparative activity (23.8%), burdock leaf extract (21%) was inferior to sodium diclofenac (36%) and exceeded the effect of quercetin (7.9%) (table 3.4).

The obtained data on the reparative activity of the studied substances are also confirmed by the number of animals in the group in which the ulcers have completely healed. In the group of animals receiving burdock sodium diclofenac, wounds were completely healed in 3 animals, in the group of rats receiving burdock leaf extract - 2 (40%), in rats receiving quercetin - in 1 animal.За середньою репаративною дією досліджувані препарати можна розмістити так: диклофенак натрію (36,0%) > екстракт листя лопуха (21%) > кверцетин (7,9%).

Thus, it can be concluded that in the model of necrotic ulcers in rats, burdock leaf extract did not show anti-alterative properties. Burdock extract has a moderate reparative activity, inferior to the reparative effect of diclofenac sodium and greater than the reparative effect of quercetin.

3.4. Study of the antiproliferative effect of a thick extract of burdock leaves on the model of cotton wool granuloma in rats

Study on the antiproliferative properties of burdock root extract was conducted on 24 purebred white male rats.

Quercetin and indomethacin, which is widely used in inflammatory-degenerative diseases of joints and connective tissue and has the most pronounced antiproliferative activity of all known NSAIDs, were chosen as comparison drugs [3, 52].

The studied drugs were administered in a therapeutic mode once a day for 7 days from the moment of implantation of a sterile cotton ball. The drugs were administered intragastrically: indomethacin in a dose of ED_{50}, which is 10 mg/kg, quercetin, burdock leaf extract - in conditionally effective doses of 50 mg/kg and 25 mg/kg, respectively.

The antiproliferative activity of the selected objects was determined by the difference in the mass of granulation-fibrous tissue with a similar indicator in animals of the control pathology group

The results of the study are shown in table 3.5.

After removal, the weight of the cotton ball in the group of animals with control pathology was 51.2 mg (table 3.5), which indicates the intensive formation of granulation tissue around the implanted ball, as well as the development of a local inflammatory process.

In all groups of treated animals, a significant decrease in proliferative processes was observed in relation to the group of control pathology, but the antiproliferative activity was different.

Table 3.5

Antiproliferative activity of burdock leaf extract on the model of cotton wool granuloma in rats (n=6)

Substances	Dose, mg/kg	Mass of granulation tissue, mg	Antiproliferative activity, %
Control pathology	–	51.2±3.1	–
Burdock leaf extract,	25.0	40.9±3.5*/**	20.1
Indomethacin	10.0	27.3±2.0*	46.7
Quercetin	50.0	42.6±2.3*/**	16.8

Note. Statistically significant differences ($p \leq 0.05$): * - in relation to control pathology, ** - in relation to indomethacin.

In animals treated with a thick extract of burdock leaves, the weight of the cotton ball decreased on average to 40.9 g, which corresponds to an antiproliferative activity of 20.1%. When using indomethacin, the mass of granulation tissue was equal to 27.3 mg, and the antiproliferative activity was 46.7%, that is, it significantly exceeded the effect of all other substances under investigation.

Quercetin helped reduce the mass of granulation tissue to 42.6 g on average, its antiproliferative activity was 16.8%, that is, in this study, quercetin exerted the least antiproliferative effect.

Based on the obtained results, according to the degree of antiproliferative activity, the studied drugs were distributed as follows: indomethacin (46.7%) > burdock leaf extract (20.1%) ≥ quercetin (16.8%).

So, it was determined that the burdock leaf extract showed a moderate antiproliferative effect on the cotton wool granuloma model, which was at the level of quercetin, but 2.3 times inferior to the effect of indomethacin.

The pronounced antiproliferative effect of indomethacin can be explained by its ability to significantly inhibit collagen synthesis [2, 3, 52]. The antiproliferative

activity of the thick extract of burdock leaves is provided primarily by sitosterol, which has antiproliferative properties [29, 32, 46, 53].

Conclusions for chapter 3

Thus, according to the results of research on pharmacological properties, it was established that the extract of burdock leaves showed an anti-exudative effect, which was inferior to diclofenac sodium (carrageenan edema) and quercetin (zymosan edema). The studied extract did not show anti-alterative activity, but had a moderate reparative and anti-proliferative effect.

CONCLUSIONS

1. The analysis of literature data shows that, despite a significant arsenal of NSAIDs, inflammatory diseases are an important medical and social problem, and their pharmacotherapy needs to be optimized.

2. One of the directions for improving the therapy of inflammatory diseases is the creation and study of new effective and safe herbal preparations with anti-inflammatory properties. One of the promising medicinal plants with potential anti-inflammatory properties is burdock large.

3. Based on the results of the research, it was found that a thick extract of burdock leaves in conditions of acute aseptic inflammation has an antiexudative effect (36.3-42.4%), which is inferior to diclofenac sodium (carrageenan edema) and not inferior to quercetin (zymosan edema). The conditionally effective dose of burdock leaf extract for anti-inflammatory activity, which is 25 mg/kg, was also determined.

4. According to the results of the work, it was also established that, on the model of acetic acid ulcers in rats, a thick extract of burdock leaves does not show anti-alterative effects, but has moderate reparative properties. Burdock leaf extract is inferior to sodium diclofenac and superior to quercetin in its reparative effect on the model of necrotic ulcers.

5. It was established that the investigated agent has a moderate (20.1%) antiproliferative effect on the cotton wool granuloma model.

6. The obtained research results can be explained by the presence of inulin, flavonoids and hydroxycinnamic acids, which have anti-inflammatory properties, in the burdock leaf extract.

7. The obtained results prove the perspective of further preclinical studies of the thick extract of large burdock leaves with the aim of creating new domestic drugs for complex therapy of inflammatory diseases.

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APPLICATIONS

APPLICATION A

STUDY OF ANTI-EXUDATIVE PROPERTIES OF THE BUDROCK LEAVES THICK EXTRACT

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Introduction. The problem of pharmacological correction of inflammation, as before, remains an urgent problem of modern medicine. Nonsteroidal anti-inflammatory drugs (NSAIDs) are drugs of first choice for the treatment of inflammatory diseases of the musculoskeletal system. However, it should be determined that despite the undoubted clinical effectiveness, the use of NSAIDs is accompanied by serious side effects related to the mechanism of their action. In connection with the above, despite the diverse assortment of anti-inflammatory agents, there is a need for drugs to correct inflammation. The search for new drugs with an unconventional mechanism of action and minimal side effects is relevant and ongoing. Phytotherapy is one of the promising areas of creating safe and effective anti-inflammatory drugs. Unlike synthetic drugs, they have a mild physiological effect and have a high level of safety. It is also worth noting that medicinal plants contain many pharmacologically active substances, which determines their wide pharmacodynamic capabilities. Burdock is one of the plants traditionally used in folk medicine to treat inflammation. It is known that burdock leaves contain ascorbic acid, carotene, rutin, hyperoside, essential oil, mucilage, tannins. Analysis of the phytochemical composition of burdock leaves allows us to predict the presence of anti-inflammatory properties in this medicinal raw material.

Aim of the study: experimental study of the antiexudative properties of a thick extract of large burdock leaves.

Materials and methods. We studied the antiexudative properties of a thick extract of burdock leaves on a model of acute aseptic inflammation in rats - zymosan edema. It is known that the metabolism of arachidonic acid can occur not only by the oxygen (cyclooxygenase), but also by the oxygen-free (5-lipoxygenase) pathway, which leads to the formation of leukotrienes. To determine the effect of burdock leaf extract on the course of the inflammatory process, the leading role in the development of which belongs to leukotrienes, it was advisable to investigate its effect on the model of zymosan edema in rats. Quercetin was chosen as a comparator, along with diclofenac sodium, because it has the ability to inhibit the 5-lipoxygenase pathway of arachidonic acid conversion and inhibit the formation of leukotrienes.

CONTINUATION OF APPLICATION A

Acute aseptic inflammation was reproduced by the introduction of 2% zymosan solution in accordance with the methodological recommendations of the Ministry of Health of Ukraine for the preclinical study of medicinal products. The phlogogenic agent was administered subplantarly in a volume of 0.1 ml per animal 1 hour after the last administration of the studied drugs. The amount of paw edema was measured using a mechanical oncometer according to A.S. Zakharevskyi in dynamics: 1, 2, 3, 4 hours after the introduction of phlogogenic substance. The antiexudative activity of the studied substances was determined by their ability to reduce the development of edema in comparison with the group of control pathology and expressed as a percentage. A thick extract of burdock leaves was administered intragastrically in doses of 25; 50 and 75 mg/kg, comparison drugs diclofenac sodium and quercetin - intragastrically in doses of 8 mg/kg and 5 mg/kg, respectively. Control animals were injected with an equivalent amount of solvent. The drugs were administered prophylactically for 4 days before the reproduction of the model pathology, the last time - 1 hour before the induction of inflammation.

Results and discussion. The introduction of a phlogogenic agent caused swelling and an increase in the volume of the limbs of experimental animals by an average of 1.2-1.7 times. Prophylactic administration of the studied substances contributed to a reliable decrease in the volume of paws, that is, they all showed anti-inflammatory effects to varying degrees. Only the extract of burdock leaves at a dose of 25 mg/kg for the first and second hours of the experiment showed a reliable act-exudative effect, which was 27% and 37.4%, respectively. Other drugs also showed only a tendency to anti-edema effect. At the third hour, burdock leaves extract in doses of 25 mg/kg (49.9%) and 50 mg/kg (45.8%) maximally reduced paw swelling. The antiexudative activity of quercetin and diclofenac sodium was in the range of 40-41.5%. Burdock leaves extract at a dose of 75 mg/kg (32.6%) was the least active. At the end of the fourth hour, quercetin (45.9%) and burdock leaves extract at a dose of 25 mg/kg (42.1%) most actively reduced the swelling of the limbs of rats. Burdock leaves extract at a dose of 75 mg/kg (33.6%) and diclofenac sodium (30.8%) were less active. The drugs are arranged in the following order according to the average act-exudative effect: burdock leaves extract, 25 mg/kg (39.1%) = quercetin (37.4%) = burdock leaves extract, 75 mg/kg (36.3%) ≥ diclofenac sodium (34.2%) ≥ burdock leaves extract, 25 mg/kg (30.6%).

Conclusions. Burdock leaves extract at a dose of 25 mg/kg showed the greatest anti-edematous effect on the zymosan edema model. This dose is conditionally effective and can be used in further studies.

APPLICATION B

КЛІНІЧНА ФАРМАЦІЯ В УКРАЇНІ ТА СВІТІ

2023

Міністерство охорони здоров'я України
Національний фармацевтичний університет
Кафедра клінічної фармакології
та клінічної фармації

The Ministry of HealthCare of Ukraine
National University of Pharmacy
Department of Clinical Pharmacology
and Clinical Pharmacy

СЕРТИФІКАТ
CERTIFICATE

№ 286

Цим засвідчується, що

This is to certify that

Dipt Charaf Eddine

брав(ла) участь у роботі Всеукраїнської науково-практичної Internet-конференції з міжнародною участю **"Клінічна фармація в Україні та світі"**, присвяченої 30-річчю заснування кафедри клінічної фармакології та клінічної фармації Національного фармацевтичного університету

16-17 березня 2023 р., м. Харків

participated in the All-Ukrainian scientific and practical Internet-conference with international participation **"Clinical pharmacy in Ukraine and the World"**, dedicated to the 30th anniversary of the Department of Clinical Pharmacology and Clinical Pharmacy of the National University of Pharmacy founding

March 16-17, 2023, Kharkiv

В.о. ректора НФаУ, проф. — **Алла КОТВІЦЬКА**

Проректор з науково-педагогічної роботи НФаУ, проф. — **Інна ВЛАДИМИРОВА**

Завідувачка кафедри клінічної фармакології та клінічної фармації, проф. — **Катерина ЗУПАНЕЦЬ**

APPLICATION C

STUDY OF ANTI-INFLAMMATORY PROPERTIES THICK EXTRACT OF THE LARGE BURDOCK LEAVES

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National University of Pharmacy, Kharkiv, Ukraine

Introduction. The problem of pharmacological correction of inflammation, as before, remains an urgent problem of modern medicine. Nonsteroidal anti-inflammatory drugs (NSAIDs) are drugs of first choice for the treatment of inflammatory diseases of the musculoskeletal system. However, it should be determined that despite the undoubted clinical effectiveness, the use of NSAIDs is accompanied by serious side effects related to the mechanism of their action. In connection with the above, despite the diverse assortment of anti-inflammatory agents, there is a need for drugs to correct inflammation. The search for new drugs with an unconventional mechanism of action and minimal side effects is relevant and ongoing. Phytotherapy is one of the promising areas of creating safe and effective anti-inflammatory drugs. Burdock is one of the plants traditionally used in folk medicine to treat inflammation. It is known that burdock leaves contain ascorbic acid, carotene, rutin, hyperoside, essential oil, mucilage, tannins. Analysis of the phytochemical composition of burdock leaves allows us to predict the presence of anti-inflammatory properties in this medicinal raw material.

Aim of the study. Experimental study of the antiexudative properties of a thick extract of the large burdock leaves.

Materials and methods. We studied the antiexudative properties of a thick extract of burdock leaves on a model of acute aseptic inflammation in rats - carrageenan edema.

The choice of the model is due to its informativeness, since at each stage of the development of inflammation, other things being equal, a certain group (or groups) of mediators participating in the development of the exudative reaction is of primary importance. Reference NSAIDs with a pronounced anti-inflammatory effect - diclofenac sodium and a plant-derived drug with proven anti-inflammatory activity - quercetin were selected as comparison drugs.

Acute aseptic inflammation was reproduced by introducing a 1% carrageenan solution in accordance with the methodological recommendations of the State Expert Center of the Ministry of Health of Ukraine for preclinical study of medicinal products. The phlogogenic agent was administered to rats subplantarly in a volume of 0.1 ml per animal 1 hour after the last administration of the studied drugs. The amount of paw edema in rats was measured using a mechanical oncometer according to A.S. Zakharevsky in dynamics: 1, 2, 3, 4, 5 and 6 hours after the introduction of carrageenan. The anti-exudative activity of the studied drugs in acute exudative inflammation was determined by the ability to reduce the development of edema in comparison with the control pathology group and was expressed as a percentage.

A thick extract of burdock leaves was administered intragastrically in doses of 25; 50 and 75 mg/kg, comparison drugs diclofenac sodium and quercetin - intragastrically in doses of 8 mg/kg and 50 mg/kg, respectively. Control animals were

injected with an equivalent amount of solvent. The drugs were administered prophylactically for 4 days before the reproduction of the model pathology, the last time - 1 hour before the induction of inflammation.

Results and discussion. The introduction of a carrageenan solution led to swelling of the hind limbs in experimental animals. Thus, in rats from the control pathology group, the paw volume increased 1.2 times after 1 hour, 1.6 times after 2 hours, 1.6 times after 3 hours, and 1.8 times after 4 hours. once, after 5 hours - 1.7 times, after 6 hours - 1.5 times. The maximum swelling was observed during 3, 4 and 5 hours and remained until the end of the study.

The introduction of the studied substances led to a significant reduction in the swelling of the limbs of the experimental animals. At 1 hour of the study, only the extract of burdock leaves at a dose of 25 mg/kg showed reliable antiexudative activity (28.5%). The activity of diclofenac sodium was 27.7%, but the changes in the volume of rat paws were not reliable. At the end of 2 hours, diclofenac sodium showed the greatest antiexudative activity (71.4%), the effect of burdock leaves extracts in doses of 25, 50 and 75 mg/kg was inferior to the effect of diclofenac (43.3%, 27.3% and 39.4%, respectively) .

At the end of the third hour, burdock leaves extract in all doses and both reference drugs showed a reliable anti-edematous effect. Diclofenac sodium was the most active, its antiexudative activity was 79.2%. Burdock leaves extract in doses of 25 and 50 mg/kg was somewhat inferior to it, the antiexudative effect was 57.8% and 45.9%, respectively. The anti-edema effect of burdock leaf extract at a dose of 75 mg/kg was equal to 38.2%. During the next hour, sodium diclofenac also showed the maximum anti-edema effect (88.4%), the anti-edema effect of burdock leaves extract at a dose of 25 mg/kg was 76.5%, the effect of burdock leaves extract at a dose of 50 mg/kg was 49.9 %, in a dose of 75 mg/kg – 59.6% Quercetin showed the least activity (29.5%). At five hour, a similar picture was observed. Diclofenac sodium showed maximum activity (78%), burdock leaves extract at a dose of 25 mg/kg was slightly inferior to diclofenac sodium, its activity was 67.2%. Burdock leaf extract in doses of 50 and 75 mg/kg at this time showed almost the same effect - 49.5% and 48.3%, respectively. At the end of the study, burdock leaves extract at a dose of 25 mg/kg (71.1%) was the most active. Other drugs were inferior to it in anti-edema effect. The effect of diclofenac sodium was 59.1%, the effect of burdock leaves extracts in doses of 50 and 75 mg/kg was 29% and 37.6%, respectively. Quercetin did not show reliable anti-exudative activity.

The studied substances can be placed in the following series according to the average anti-exudative activity: diclofenac sodium (67.3%) > burdock leaves extract, 25 mg/kg (57.4%) > burdock leaves extract, 75 mg/kg (42.4%) ≥ burdock leaves extract, 50 mg/kg (37.1%) > quercetin (24.8%).

Conclusions. Burdock leaves extract at a dose of 25 mg/kg showed the greatest anti-edematous effect on the carrageenan edema model. This dose is conditionally effective in terms of anti-inflammatory activity and can be used in further studies.

APPLICATION D

Ministry of health of Ukraine
Ministry of education and science of Ukraine
National university of pharmacy
Pharmaceutical chemistry department
Medicinal chemistry department
General chemistry department
Analytical chemistry and analytical toxicology department

CERTIFICATE №023

This is to certify that

Dibt Charaf Eddine

participated in the International Internet Conference
'Modern chemistry of medicines'
(duration - 8 hours)
May 18, 2023, Kharkiv, Ukraine

Certificate of the State Scientific Institution 'Ukrainian Institute of Scientific and Technical Expertise and Information' No. 550 dated 19.12.2022

Acting rector of the NUPh, prof. — Alla KOTVITSKA

Vice-Rector for Research and Development, prof. — Inna VLADIMIROVA

Ф А 2.2.1-32-366

National University of Pharmacy

Faculty for foreign citizens' education
Department of Pharmacology and Pharmacotherapy
Level of higher education master
Specialty 226 Pharmacy, industrial pharmacy
Educational program Pharmacy

APPROVED
The Head of Department
of Pharmacology and
Pharmacotherapy

_____
Sergey SHTRYGOL'
«21» of September 2022

ASSIGNMENT

FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Charaf Eddine DIBT

1. Topic of qualification work: «Study of the anti-inflammatory action of Burdock leaves thick extract», supervisor of qualification work: Kateryna SHCHOKINA, doctor of Pharmacy, prof.

approved by order of NUPh from "06" of February_2023 № 35

2. Deadline for submission of qualification work by the applicant for higher education: september 2022.

3. Outgoing data for qualification work: The qualification work is devoted to studying the anti-inflammatory properties of a thick extract of large burdock leaves. An experimental study of the anti-exudative, anti-alterative, anti-proliferative and reparative effect of a thick extract of burdock leaves was conducted in order to assess the feasibility of creating preparations based on it for the prevention and complex therapy of inflammatory diseases. The work consists of an introduction, the main part (literature review, materials and methods, own research), conclusions, a list of literature sources).

4. Contents of the settlement and explanatory note (list of questions that need to be developed):
analysis of domestic and foreign literature on this topic; theoretical substantiation of the relevance and expediency of optimizing the pharmacotherapy of inflammatory diseases by including in complex therapy new herbal preparations with a complex effect on various pathogenetic links of the disease; experimental study of the anti-inflammatory properties of a thick extract of burdock leaves on models of acute aseptic inflammation, acetic acid ulcers and cotton wool granuloma in rats; analysis of the obtained results regarding the feasibility of creating original domestic anti-inflammatory drugs based on it.

5. List of graphic material (with exact indication of the required drawings): tables – 6

6. Consultants of chapters of qualification work

Chapters	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
1	Kateryna SHCHOKINA, professor of higher education institution of pharmacology and clinical pharmacotherapy department	Kateryna SHCHOKINA, 21.09.2022	Charaf Eddine DIBT, 21.09.2022
2	Kateryna SHCHOKINA, professor of higher education institution of pharmacology and clinical pharmacotherapy department	Kateryna SHCHOKINA, 21.09.2022	Charaf Eddine DIBT, 21.09.2022
3	Kateryna SHCHOKINA, professor of higher education institution of pharmacology and clinical pharmacotherapy department	Kateryna SHCHOKINA, 21.09.2022	Charaf Eddine DIBT, 21.09.2022
4	Kateryna SHCHOKINA, professor of higher education institution of pharmacology and clinical pharmacotherapy department	Kateryna SHCHOKINA, 21.09.2022	Charaf Eddine DIBT, 21.09.2022

7. Date of issue of the assignment: "21" of September 2022

CALENDAR PLAN

№ з/п	Name of stages of qualification work	Deadline for the stages of qualification work	Notes
1.	Conducting a literature review on the issues of the work.	December 2022	**done**
2.	Conducting of studies	January-February 2023	**done**
3.	Writing and preparation of the manuscript of the qualification work	March-April 2023	**done**
4.	Submitting the final version of the work to the academic supervisor and receiving feedback from him	April 2023	**done**
5.	Registration of the work and accompanying documents and submission to the Examination Committee of the NUPh.	April 2023	**done**

An applicant of higher education _____ Charaf Eddine DIBT

Supervisor of qualification work _____ Kateryna SHCHOKINA

ВИТЯГ З НАКАЗУ № 35
По Національному фармацевтичному університету
від 06 лютого 2023 року

нижченаведеним студентам 5-го курсу 2022-2023 навчального року, навчання за освітнім ступенем «магістр», галузь знань 22 охорона здоров'я, спеціальності 226 – фармація, промислова фармація, освітня програма – фармація, денна форма здобуття освіти (термін навчання 4 роки 10 місяців та 3 роки 10 місяців), які навчаються за контрактом, затвердити теми кваліфікаційних робіт:

Прізвище студента	Тема кваліфікаційної роботи		Посада, прізвище та ініціали керівника	Рецензент кваліфікаційної роботи
• **по кафедрі фармакології та фармакотерапії**				
Дібт Шараф Едділ	Вивчення протизапальної дії густого екстракту листя лопуха великого	Study of the anti-inflammatory action of Burdock le aves thick extract	Проф. Щокіна К.Г.	Доц. Отрішко І.А.

Підстава: подання декана, згода ректора

Ректор

Вірно. Секретар

Ф А2.8-47-110

ВИСНОВОК

Комісії з академічної доброчесності про проведену експертизу щодо академічного плагіату у кваліфікаційній роботі здобувача вищої освіти

№ 112575 від « 25 » квітня 2023 р.

Проаналізувавши випускну кваліфікаційну роботу за магістерським рівнем здобувача вищої освіти денної форми навчання Дібт Шараф Еддін, 5 курсу, _____ групи, спеціальності 226 Фармація, промислова фармація, на тему: «Вивчення протизапальної дії густого екстракту листя лопуха великого / Study of the anti-inflammatory action of Burdock leaves thick extract», Комісія з академічної доброчесності дійшла висновку, що робота, представлена до Екзаменаційної комісії для захисту, виконана самостійно і не містить елементів академічного плагіату (компіляції).

Голова комісії,
професор **Інна ВЛАДИМИРОВА**

8%

29%

Ф А 2.2.1-32-353

REVIEW

of scientific supervisor for the qualification work of the master's level of higher education of the specialty 226 Pharmacy, industrial pharmacy

Charaf Eddine DIBT

on the topic: «Study of the anti-inflammatory action of Burdock leaves thick extract»

Relevance of the topic. The problem of pharmacological regulation of inflammation is still an urgent problem of modern medicine. First-line drugs for the treatment of inflammatory diseases are non-steroidal anti-inflammatory drugs (NSAIDs). It is also known that despite high clinical effectiveness, NSAIDs have a number of undesirable effects. Even short-term use of these drugs leads to adverse reactions that can pose a serious threat to the patient's health. In connection with the above, despite the diverse assortment of anti-inflammatory agents, the search for new drugs with an unconventional mechanism of action and minimal side effects is constantly being conducted. One of the ways to optimize anti-inflammatory therapy is the inclusion of herbal preparations in the complex therapy of inflammatory diseases. An experimental study of the anti-inflammatory properties of a thick extract of large burdock leaves was conducted by a master's student of the department in the qualification work.

Practical value of conclusions, recommendations, and their validity. The conclusions and recommendations formulated in the qualification work correspond to the research objectives. The obtained conclusions are of practical value for pharmacists and practicing doctors to optimize the complex therapy of inflammatory diseases due to the inclusion of drugs based on a thick extract of burdock leaves. The obtained research results were highlighted by the author in 2 theses and tested at 2 scientific and practical conferences.

General conclusion and recommendations on admission to defend. The work is performed in full, designed in accordance with the current requirements for the

qualification works at the National University of Pharmacy, and can be recommended for submission to the SEC for further defense.

Scientific supervisor _____ Kateryna SHCHOKINA

«3» of April 2023

Ф А 2.2.1-32-356

REVIEW

for qualification work of the master's level of higher education, specialty 226 Pharmacy, industrial pharmacy

Charaf Eddine DIBT

on the topic: «Study of the anti-inflammatory action of Burdock leaves thick extract»

Relevance of the topic. Despite the significant progress achieved in the treatment of inflammatory diseases, their pharmacotherapy remains one of the most difficult issues in modern medicine. The main group of drugs used in rheumatology are nonsteroidal anti-inflammatory drugs. It is known that despite the undoubtedly proven clinical effectiveness, the use of NSAIDs has certain limitations. The above indicates the need to optimize the pharmacotherapy of inflammatory diseases. One of the important directions of improving anti-inflammatory therapy is the inclusion in the treatment regimen of drugs from other pharmacological groups that have anti-inflammatory properties.

Theoretical level of work. In the work submitted for review, the author elaborated a large volume of scientific sources on the relevant topic. For the first time, an experimental study of the main components of the anti-inflammatory effect of a thick extract of large burdock leaves was conducted. The author of the paper studied the anti-exudative, anti-alterative, reparative and anti-proliferative effect of a thick extract of burdock leaves on various models of inflammation, adequate for human diseases. The obtained results made it possible to draw a conclusion about the expediency of including these drugs in anti-inflammatory therapy. The conclusions made by the author and the provisions of the qualification work are based on a sufficient number of observations.

Author's suggestions on the research topic. Based on the obtained results, the author proposed to carry out further in-depth preclinical studies of the thick extract of

large burdock leaves with the aim of creating new domestic herbal drugs with anti-inflammatory action.

Practical value of conclusions, recommendations, and their validity. The conclusions and practical recommendations proposed by the applicant are based on sufficient data obtained in the course of the conducted research, thorough analysis, and generalization of results. The results obtained can be used by pharmacists and physicians to optimize the pharmacotherapy of cardiovascular diseases.

Disadvantages of work. No significant shortcomings were identified in the work, however, it can be noted: individual grammatical, stylistic, and technical errors; Some tables are too large and it would be more expedient to place them in applications. These do not fundamentally change the assessment of the work and do not reduce its scientific and practical significance.

General conclusion and assessment of the work. The work meets the requirements for qualification work in NUPh and can be recommended for defense.

Reviewer _____ assoc. prof. Inna OTRISHKO

«7» April 2023

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ
Витяг з протоколу № 14
від 11 квітня 2023 року
м. Харків
засідання кафедри фармакології та фармакотерапії

ПРИСУТНІ: зав. каф. проф. Штриголь С.Ю., проф. Кіреєв І.В., проф. Деримедвідь Л.В, проф. Бутко Я.О., проф. Щокіна К.Г., доц. Бєлік Г.В., доц. Рябова О.О., доц. Жаботинська Н.В., доц. Куценко Т.О., доц. Таран А.В., доц. Матвійчук А.В., доц. Савохіна М.В., доц. Степанова С.І., ас. Кононенко А.В., ас. Толмачова К.С., ас. Цеменко К.В., Адлер Б.А., Чубар`ян Ю.І., Барзак Д.Т., Краснораменська О.В., Шульга Ю.М., Рубан Я.В., Суровцева Д.О., Леонова Я.І., Заворотько Д.І., Вороніна А.О., Давидов Е.М., Шостенко К.В., Дібт Шараф Еддін, Жудат Ікрам, Алауі Абдаллауі Яссін, Буррус Ахлам, Ель Хамді Мохаммед, Меллоукі Хамза, Іфтахі Яссін, Карім Ашраф, Айнау Умайма, Елбадауі Хажар, Ель Хайель Хаджар, Толбі Ель Мехді, Беналлал Зінеб, Бенсаід Мохаммед, Ел-Жамаі Сальма, Ельбахаджі Раіхана, Бензід Ясіне, Кадді Каутар.

ПОРЯДОК ДЕННИЙ:
Розгляд кваліфікаційних робіт здобувачів вищої освіти для подання робіт до Екзаменаційної комісії.

СЛУХАЛИ:
Здобувача вищої освіти Дібт Шараф Едділа зі звітом про проведену наукову діяльність за темою кваліфікаційної роботи: «Вивчення протизапальної дії густого екстракту листя лопуха великого».

УХВАЛИЛИ:
Кваліфікаційну роботу розглянуто. Здобувач вищої освіти Дібт Шараф Еддін допускається до захисту даної кваліфікаційної роботи в Екзаменаційній комісії.

Завідувач кафедри фармакології
та фармакотерапії, проф. _____ Штриголь С.Ю.
Секретар кафедри фармакології
та фармакотерапії, ас. _____ Кононенко А.В.

Ф А2.2.1-32-042

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ПОДАННЯ
ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувач вищої освіти Шараф Еддін ДІБТ до захисту кваліфікаційної роботи
за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньою програмою Фармація
на тему: «Study of the anti-inflammatory action of Burdock leaves thick extract».

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Світлана КАЛАЙЧЕВА /

Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти Шараф Еддін ДІБТ виконав весь необхідний обсяг робіт. Магістерська робота може бути рекомендована до подачі в ЕК НФаУ для подальшого захисту кваліфікаційної роботи.

Керівник кваліфікаційної роботи

_____ Катерина ЩОКІНА

« 3 » квітня 2023 року

Висновок кафедри про кваліфікаційну роботу

Кваліфікаційну роботу розглянуто. Здобувач вищої освіти Шараф Еддін ДІБТ допускається до захисту даної кваліфікаційної роботи в Екзаменаційній комісії.

Завідувач кафедри
фармакології та фармакотерапії

_____ Сергій ШТРИГОЛЬ

«11» квітня 2023 року

Qualification work was defended

of Examination commission on

« ___ » _____ 2023

with the grade _____

Head of the State Examination commission,

DPharmSc, Professor

_____ / Oleh SHPYCHAK /