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YUSUPOVA SH.Q.
UMURZAKOVA R.Z.

EFFECT OF PREPARATIONS OF BARBERRY VULGARIS FOR THROMBOCYTOPOIESIS

(Monography)

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Compiled by:

Yusupova Shaxnoza Qodirjonovna	Doctor of Medical Sciences, Associate Professor, Head of the Department of Hospital Therapy and Endocrinology
Umurzakova Roxila Zokirovna	Associate Professor of the Department of Hospital Therapy with a Course of Endocrinology, Andijan State Medical Institute.

Reviewers:

Bobojonova Shaira Akzamovna	Professor of the Department of Hematology, Transfusiology and Laboratory Science of the Tashkent. Medical Academy.
Salakhiddinov Zuxriddin Salaxiddinovich	Professor, head of the Department of Doctors Training general practice, doctor of medical sciences.

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Secretary of the ASMI Council,
Candidate of Medical Sciences,
Associate Professor **N.A. Nasriddinova**

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Аннотация

Мазкур монография оддий зирк препаратларининг тромбоцитопоэзга таъсирини ўрганишга ва уларнинг таъсир қилишнинг мураккаб механизмларини ёритишга бағишланган. Монографияда клиник ва экспериментал равишда оддий зирк препаратларининг тромбоцитопоэзга таъсири аниқланди, биринчи марта оддий зирк препаратларини тромботцитопоэзга стимулловчи сифатида қўлланлиши илмий асосланди. Экспериментал маълумотлар асосида турли хил сабаблар орқали келиб чиқадиган тромботцитопения билан оғриган беморларни оддий зирк препаратлари билан даволашнинг янги усули ишлаб чиқилди. Муаллиф экспериментал ва биологик жиҳатдан оддий зирк препаратлари қон зардобида тромботцитларни стимулловчи омил - тромботцитопоэтинни оширишини исботланган.

Аннотация

В данной монографии представлены результаты специального клинически-экспериментального изучению влияния препаратов барбариса обыкновенного на тромбоцитопоэз и выявлены сложные механизмы их действия, а также изучен характер влияния препаратов барбариса обыкновенного на тромбоцитопоэз у экспериментальных животных. Препарат увеличивает выработку тромбоцитопоэтинов, играющих главную роль в регулировании роли тромбоцитопоэза. Это доказано биологическим методом.

Annotation

This monograph by R.Z. Umurzakova is devoted to the study of the effect of common barberry preparations on thrombopoiesis and the explanation of the complex mechanisms of their action. The monograph clinically and experimentally established the effect of common barberry preparations on thrombocytopoiesis and scientifically substantiated the use of common barberry preparations as a thrombocytopoiesis stimulator. On the basis of experimental data, a new method for the treatment of patients with thrombocytopenia of various origins with preparations of common barberry has been developed. The author experimentally and biologically proved that preparations of common barberry increase the platelet-stimulating factor, thrombocytopoietin, in the blood serum.

CONTENT

INTRODUCTION

TOPICALITY OF THE PROBLEM.

The problem of bleeding has been and remains an urgent task of modern medicine, since bleeding proved to be the one of the severe complications in various diseases and conditions of the body: in hematology, obstetric pathology, surgery, infectious diseases, otorhinolaryngology, in case of an overdose of direct and indirect anticoagulants, disseminated wounds, intra-vascular coagulation, gastrointestinal, uterine, wound, parenchymal bleeding, which require timely doctors' intervention and the use of effective and reliable hemostatic agents of general and local action [23,40,141].

It is known that 85% of bleeding observed in medical practice occur due to a decrease in the number of platelets or their functional insufficiency. Chemicalization and industrialization of the national economy result into a sharp increase in diseases associated with impaired thrombopoiesis (16,64,163).

Hemorrhagic syndrome is one of the leading clinical manifestations of a number of diseases of the blood system (57,77,12). Hemorrhagic diathesis occurs in children; young women, more often at the most labour-capable age, which, in its turn, has a great medical and social significance of this problem.

There are no specific drugs for the treatment of diseases associated with disorders of the platelet-megakaryocytic system. The drugs currently used in the clinic for the treatment of such diseases are not always effective and often dangerous due to a number of complications. Insufficiency of the applied therapy and epidemiology of diseases accompanied by thrombocytopenia make it understandable and justified to search for new highly effective specific agents which can regulate thrombocytopenia.

The use of herbal medicines proved to be one of the perspective directions in the treatment of various diseases, including thrombocytopenia. According to K. Kayumov (1971), the advantages of treatment with medicinal plants are that the structure of medicinal plants is closer to the human body than a chemical preparation.

Besides, they are low-toxic and enter the living cell without conflict. Therefore, the search and use of drugs from the domestic flora is justified.

The flora of Uzbekistan is rich in wild useful plants, the most valuable of them for actual use are constantly studying and identifying. One of these plants is the common barberry (B. Vulgaris). Abu Ali ibn Sina (Avicenna-(4) pointed out the healing properties, including hemostatic. The alkaloid berberine, tinctures and decoction of common barberry is used to stop uterine bleeding (6), which suggests its stimulating effect on thrombocytopoiesis.

This monography is devoted to the study of the effect of common barberry preparations on thrombopoiesis and the description of complex mechanism of their action.

The following OBJECTIVES have been set to achieve this goal:

I. To study the nature of the effect of common barberry preparations on thrombopoiesis in experimental animals:

a) to study the effect of common barberry preparations on the number of thrombocytes in the peripheral blood of rats;

b) to study the effect of preparations of common barberry on the number of megakaryocytes in the bone marrow of rats;

c) to study the possible mechanism of action of common barberry preparations on thrombopoiesis.

II. To study the effect of common barberry preparations on the number of platelets in peripheral blood in patients with thrombocytopenia of various origins:

b) in patients with anemia with symptomatic thrombocytopenia;

c) in patients with hematopoietic depression;

d) in patients with malignant lymphomas;

e) in patients with liver disease with symptomatic thrombocytopenia.

2. To study the effect of common barberry preparations on the adhesive-aggregation and disaggregation function of platelets.

3. To study the effect of common barberry preparations on the primary bleeding time and on the time of capillary blood clotting.

This work is an experimental clinical and experimental study of the effect of common barberry preparations on thrombopoiesis.

The use of common barberry preparations as a thrombopoiesis stimulator has been scientifically approved. A new method for the treatment of patients with thrombocytopenia of various origins with barberry preparations has been developed on the basis of experimental data.

It has been established that in patients with ITP and symptomatic thrombocytopenia adhesive-aggregation activity increases, platelet disaggregation ability decreases, bleeding time shortens and capillary blood clotting time accelerates under the influence of common barberry preparations.

CHAPTER I. THE ROLE OF THROMBOCYTES IN HEMOSTASIS

(Literature Review)

I.I. Modern concepts thrombocytes and their functions.

Under normal conditions thrombocytes circulate in the bloodstream in the form of round or oval disc-shaped plates with a diameter of 2-5 microns limited by a three-layer membrane of 8 microns thick, in which a peripheral unstructured zone and a granular central one, colored in blue color-hylomer, can be distinguishable (35,64).

There is a negative charge on the surface of platelets that prevents their aggregation with each other, adhesion to the vascular endothelium and other blood elements. Factors, that reduce the platelet charge, significantly disrupt the bioelectric balance in the blood system - the vascular wall and the stability of the suspension of corpuscular elements, which ultimately leads to their intravascular aggregation (17,22,127). Compounds that possess a positive charge, for example, polylysine, also contribute to thrombocytes' adhesion; apparently, an increase in the negative charge of the platelets

should contribute to the stability of their state, and this assumption would be one of the ways of regulating the functional activity of thrombocytes (35,64,163).

It has been established that thrombocytes recently detached from megakaryocytes and entering the bloodstream, proved to be of very large size; under physiological conditions they have a greater metabolic potential and a greater ability to hemostatic reactions. Large forms of thrombocytes (mega thrombocytes) have an increased adhesive and aggregation ability, a high level of oxidative phosphorylation and higher glycogen content (17).

Along with mega thrombocytes, there are also small forms of platelets that release an insignificant amount of factor 4 and, in comparison with mega thrombocytes, have lower metabolic potential as well as lower functional activity.

Direct correlation between the number of large forms of thrombocytes in the peripheral blood and the number of megakaryocytes in the bone marrow in hematological diseases associated with increased destruction and utilization of platelets has been noted. (27,39,57,98).

Thrombocytes not only form a thrombus at the first stage of hemostasis, but also actively participate in all stages of coagulation. They play an important role in blood clot retraction, which is performed by the platelet enzyme thrombostenin (102). It is assumed that platelets are involved in inflammatory and immunological reactions (76,11).

Platelets are capable to release substances that increase vascular permeability and involved in the body's defense response (115).

An increase in the functional activity of platelets leads to their intravascular aggregation, thrombosis and thromboembolism; a decrease in the number of platelets can result into hemorrhage.

Strong physiological activators of platelet aggregation

Proved to be ADP from the damaged vascular wall and erythrocytes in the hemostasis zone, as well as adrenaline, thrombin and a number of other substances.

D. Aranson (1976) provides evidence of the multi-stage action of thrombin. It begins with the release of peptides A and B from fibrinogen, and then the active peptide from the factor XIII catalytic subunits. This, in turn, increases the activity of factors V and VII, resulting in the excitation of processes leading to thrombocytes' aggregation and the release reaction (35).

ADP plays an important role in the formation of thrombocytes' thrombus (64,163). The source of ADP proved to be the undamaged vessel wall, endothelial cells and erythrocytes undergoing maceration in the hemostasis zone. Most of all, ADP is released into the environment by the platelets themselves, which is referred to as the "release reaction".

At a low concentration of ADP, aggregation proceeds in stages; the initial phase - a change in the forms of platelets, aggregation, disaggregation and a return to the initial sensitivity of ADP.

An increase in ADP concentration leads to aggregation, which occurs at a high rate and proved to be irreversible. This final phase is associated with the "release reaction" and depends on calcium ions and plasma co-factor. Co-factor for ADP aggregation is fibrinogen. In case of an excess of calcium ions ADP aggregation is inhibited. Magnesium ions are necessary for aggregation process.

Serotonin possesses less expressed effect than ADP, it causes a change in the shape of the cell and a reversible reaction and only thrombin and collagen result into the secretion of substances from a-granules and perform the "basic reaction" of thrombocytes at the most important stage of thrombus formation and bleeding standstill (102).

It has been experimentally proved that ADF changes the shape of cells, aggregation and release of arachidonic acid occurs under its influence. The degree of ADF influence may be different; if prostaglandin and thromboxane synthesis is inhibited, then ADF affects the formation and aggregation of thrombocytes.

The "release reaction" runs in two phases: the first - serotonin, ADP, adrenaline, lipoprotein factor 3, antiheparin factor 4, etc. are secreted from thrombocytes. In the second phase adenine nucleotides and acid hydrolases are

released. The mechanism of regulation of the first and second phases of the "release reactions" is different. It was proved by the fact that this mechanism has an evident effect on the inhibition of the "release reaction" (first phase) and does not affect the second phase (163).

The process of regulation of the "release reaction" is complex and not enough studied. In some cases of hereditary and developed forms of thrombocytes' pathology, related to "disaggregation thrombocytopathy", the first phase of the "release reaction" is disrupted, resulted into interruption of the process of platelet aggregation at the earliest stages of hemostatic plug formation. Disappearance of the second wave of aggregation under the influence of ADP and adrenaline proved to be characteristic features of these forms. In other forms of platelet hemostasis, for example, in Glanzmann's thrombosthenia, aggregation is impared, but the "release reaction" is largely preserved in case of thrombocytes' contact with collagen. The second phase of the "release reaction" is disrupted in some types of thrombocytes' pathology (18).

Existence of mechanisms that suppress thrombocytes' activity is assumed along with the stimulation of the hemostatic function of platelets (35,110). Inhibitors of platelet adhesion and aggregation proved to be prostaglandin (PgJ2), a product of the intima and other layers of the vascular wall. PgJ2 inhibits the formation of a parietal thrombus by suppressing the adhesion of platelet aggregation. PgJ2 inhibitory effect is associated with its stimulating effect of platelets' adenailate cyclase, which causes an increase in basal cyclic AMP (CAMP). Moreover, PgJ2 prevents changes in the shape of thrombocytes, which is a necessary condition for adhesion and aggregation (121, 142).

The hemostatic function of thrombocytes also includes contractile properties. These properties lead to the further compaction of the thrombus. Microtubules, microfilaments and submembrane filaments are also included into the elements of the thrombocytes' contractile system. Peripheral microtubules maintain the discoid shape of circulating platelets (141), take part in the displacement of granules towards the

center of the thrombocyte under the action of aggregating agents and thereby contribute to the release of granules (109).

Recent research has proved the presence of an actomyosin-like protein called thrombostenin which was classified as a contractile protein in thrombocytes (116).
Electron microscopic investigations have shown that part of thrombosthenin is located in the cytoplasm, its another portion is connected with the surface membrane of the cell (64,126,152). Membrane thrombostenin is called S-thrombostenin. It constitutes 6-10% and cytoplasmic S-thrombosthenin 90-94% of the total thrombocytes' contractile protein (167).

Thrombostenin can be present in thrombocytes in relaxed and contracted states. Electron microscopic research has shown that thrombostenin in the form of fibrils is attached to the cytoplasm of the platelet's cell membrane.
Data about the formation of thrombostenin in megakaryocytes is available (17, 22, 35) and, according to these authors, it can be synthesized in thrombocytes using RNA transfer, despite the absence of a nucleus in these cells.

The study of the physicochemical properties of thrombostenin allowed to attribute them into the group of actomyosin-like proteins. Thrombostenin consists of 2 subunits, one of which is an analog of actin (A-thrombostenin), the other is myosin (M-thrombostenin). Thrombosthenin in a relaxed insoluble condition acquires contractile activity under the action of Ca, Mg and ATP ions (50,106).

Thrombostenin plays an important role in the implementation of all stages of primary hemostasis. When platelets are activated, thrombostenin initiates a contractile contribution involving Ca ions. It serves as a receptor for thrombin, which induces the release reaction and platelet aggregation (107, 126). With the thrombostenin decreasing thrombocytes converge in the aggregate, which becomes even more compacted and becomes impermeable for the blood.

The retraction of a blood clot proved to be the completion of a complex complex of biochemical, morphological and dynamic transformations in the processes of hemocoagulation, hemostasis and fibrinolysis. It has been stated that the

main role in the process of retraction is played by thrombocytes containing thrombosteinin-actomyosin-like protein capable of contracting (155).

In clot retraction, two phases are distinguishable - physical and chemical.

Physical retraction is the mechanical adhesion of thrombocytes to the structural elements of the clot; it begins immediately after the end of the chemical processes - the formation of fibrin thrombocyte structure (FTS). The chemical phase begins immediately with the onset of blood coagulation (22, 145). Clot retraction depends on the environment of ions where the FCS is formed. K, Na, Mg ions increase the retraction of the blood clot, and Ca ions, depending on the concentration, either stimulate the retraction of plasma clot or inhibit it (24,145).

Retraction of the FTS of the blood and plasma clot result into a more rapid process of bleeding standstill, as well as rapid healing of wounds and tissues (145).

Adsorption and transport functions are also characteristic for thrombocytes. The adsorptive activity of platelets is related to their morphological integrity; therefore, some researchers consider it as one of the indicators of cell viability (42,137).

The adsorption activity of platelets allows the thrombocytes to concentrate a significant amount of active factors of the blood coagulation system on their surface as well as other endogenous platelet factors.

Other substances, predominantly of a protein nature, surround thrombocytes with a thin outer layer, forming a layer of the plasmatic atmosphere (35,154). Branching channels penetrate into platelets deeply, the main function of which is the transport of substances between platelets and blood plasma (27,141).

In recent years, much attention has been paid to studying the role of thrombocytes in the body's immune reactions. Antigen-antibody immune complexes can cause the release of catecholamines and adenine nucleotides, thrombocyte’s aggregation and formation of aggregates with the participation of calcium ions at a temperature of 37°C. This fact indicates the presence of receptors for immune agents in platelets (95).

Immune reactions affect the level of thrombocytes in the bloodstream; thrombocytopenia can develop without activation of the blood coagulation system

and damage to the vascular wall. Clinical observations have demonstrated that in case of viral infections and hypersensitivity to drugs thrombocytopenia is caused by antigen-antibody complex circulating in the bloodstream.

The “release reaction” that occurs in response to immunity is accompanied by a release reaction and does not depend on the presence of calcium ions (113).

The presence of oxygen, iron, and copper acceptors in thrombocytes suggests that platelets are activators of respiratory groups and groups of the dehydrogenated system. Spectral analysis of platelets confirmed this phenomena which revealed absorption bands characteristic of respiratory enzymes. The ability of thrombocytes’extract to oxidize cytochrome reduced by hydrogen sulfate was demonstrated. The above-mentioned data give the possibility to conclude that thrombocytes have functions which are very important for the normal functioning of the body, the impairment of which results into various conditions of thrombocytopenia, thrombocytopathy and bleeding.

I.2. Thrombocytopenia of various origin, methods of treatment

Thrombocytopenia is a decrease in the number of thrombocytes in peripheral blood that occurs in various diseases and pathological conditions. It usually manifests itself as increased bleeding for platelets participate in the process of hemostasis. A decrease in the number of thrombocytes is often associated with changes in their structure and function.

They are differentiated as hereditary and developed, immune and non-immune forms of thrombocytopenia.

Immune forms of thrombocytopenia are divided into four groups:

1. Alloimmune, in which the destruction of thrombocytes is associated with incompatibility in one of the blood group systems, either in connection with the transfusion of foreign thrombocytes to the recipient in the presence of antibodies against them, or in connection with the penetration of antibodies to the child from a

mother previously immunized with an antigen that she does not possess, but available to the child.

2. Transimmune, in which autoantibodies from a mother suffering from autoimmune thrombocytonenia penetrate the placenta and result into thrombocytopenia in the child.

3. Heteroimmune, associated with a impairment of the antigenic structure of the thrombocyte under the influence of a virus or the appearance of a new antigen or hapten.

4. Autoimmune, associated with the production of antibodies in the body against its own autoantigens.

Immune forms of thrombocytopenia are quite common; heteroimmune versions are mostly occurred in the children, autoimmune forms occur in the adults.

Immune forms of thrombocytopenia can be divided into the following groups depending on which antigen the antibodies are directed against:

a) antibodies against thrombocyte's antigen;

b) antibodies against megakaryocyte antigen or against the common precursor antigen of thrombocytes, leukocytes and erythrocytes.

According to some data (29.95), there are 4.5 males and 7.5 females per 100,000 population suffering from autoimmune thrombocytopenia, which is often called idiopathic thrombocytopenic purpura (ITP). Most clinicians believe that the cause of ITP is a breakdown of immunological tolerance (51, 95, 151).

Some researchers (2, 6, 124) prove the existence of a certain genetic predisposition to autoimmune blood diseases, namely ITP.

Studies of thrombocytes with markers have demonstrated that all cases of thrombocytopenic purpura show a dramatic shortening of platelets' lifespan to several hours instead of 7–10 days (106, 115).

The increase of megakaryocytes and hyperproduction of thrombocytes are associated with an increase in the number of thrombocytopoietins in response to a low platelets' count.

In addition to thrombocytopoietin, a thrombocytopenic factor called thrombocytopenin was found in patients with ITP. The amount of thrombocytopenins is increased in patients with ITP. ITP is believed to be an autoimmune disease of the blood system associated with autoantibodies that result into platelets' destruction (35, 64, 163).

According to J.K. Bach autoimmunity proved to be a paradoxical physiological phenomenon that causes many serious diseases. The pathogenesis of these diseases may involve the preservation of physiological autoimmunity or the appearance of autoreactive clones that produce antibodies (97,175).

By studying the mechanism of the appearance of anti-thrombocytes' antibodies, many researchers have proved that the anti-thrombocytes' factor is not an immune complex, but F-receptor fragment of IgG - the antibody nonspecifically binds to the platelet (97, 101,151).

According to K. Oda's research (1989), quantitative analysis of the level of anti-thrombocytes' antibodies and their specificity confirm the assumption that in case of ITP, autoantibodies are not produced in relation to any single protein, but they have specificity to many AGTs, including both proteins and lipid components.

The ability of platelet antibodies to specifically bind megakaryocytes resulted from the presence of common antigenic determinants between thrombocytes and megakaryocytes (139).

It was stated that it was the spleen that produce anti-thrombocytes' antibodies; they have been eluted from spleen extracts (59,116). The authors concluded that as a result of culturing spleen sections in a medium containing marked amino acids globulin which is 5 times more actively adsorbed on the surface of donor platelets than globulin obtained by culturing sections of control spleens has been produced.

As established by a number of studies, after the removal of the spleen the main site of formation of anti-thrombocytes'antibodies in patients with ITP (50% of cases)proved to be the bone marrow (59, 130).

Thrombocytes' destruction occurs in three organs of the reticular-endothelial system: the spleen, the liver and bone marrow. In case of ITP, antibodies are directed

against thrombocyte and megakaryocyte antigens, but in the bone marrow, both destruction of platelets and suppression of thrombocytopoiesis can occur. 4-5 times more thrombocytes are produced in patients with ITP compared to normal, and only half of them enter the circulation, which means that platelets are destroyed inside the bone marrow.

Without explaining in detail the existing numerous hypotheses about the occurrence of autoimmune thrombocytopenia, it can be noted that at present the most probable opinion is that the pathological process of most forms of autoimmune thrombocytopenia is based on a breakdown of immunological tolerance to one's own antigen.

The clinical picture of ITP has been well studied and described in detail by many clinicians (62, 82, 146,159).

Thrombocytopenic hemorrhagic syndrome is characterized by

skin hemorrhages, bleeding of mucous membranes.

Skin hemorrhages can take the form of ecchymosis, they are more often observed on the limbs, trunk (mainly on its anterior surface), hemorrhages are often observed at injection sites.

Petechial rashes most often occur on the legs. Hemorrhages sometimes occur on the face, in the conjunctiva of the eyes and on the lips. The appearance of such hemorrhagic rashes proved to be a serious symptom indicating the possibility of hemorrhages in the brain.

Hemorrhagic syndrome proved to be the leading one in case of ITP and appears more often from the onset of the disease. Patients are admitted to the hospital at the height of their illness, which determines the severity of their condition (84,117, 156).

Clinical manifestations depend on the form of the disease. Acute and chronic forms of ITP are differentiated. According to most clinicians (12, 84, 156, 160), the chronic form includes diseases lasting more than 6 months.

Some authors (22, 23, 56) demonstrate that the chronic form of idiopathic thrombocytopenia is essentially autoimmune, and the acute form is heterommune

thrombocytopenia; but they propose that heterommune thrombocytopenia can run a chronic course and, on the contrary,in half of patients with autoimmune thrombocytopenia the first clinical manifestations were acute (55). The acute onset of the chronic form of ITP is sometimes accompanied by an elevation of temperature up to 37-38°C, general malaise, lethargy and loss of appetite. Then skin hemorrhages or bleeding from the nose, gums and other organs occur.

The appearance of profuse hemorrhages, especially in non-typical places, headache, nausea, vomiting, the first manifestations of paresis and paralysis are considered to be the serious symptoms indicating the possibility of cerebral hemorrhage (12,31,52). Impairment of the nervous system in thrombocytopenic purpura can depend on both hemorrhages and severe allergization of the brain; sometimes it can be the first symptom of the disease (84).

Hemorrhage is the second most common symptom of ITP, where nosebleeds (40% of patients with acute and 75% with chronic ITP) mostly occur; bleeding from the gums (4.8%), gastrointestinal (8.4%).), hematuria (9.6%) are less common - (108).

Often bleeding from the tooth socket proved to be a manifestation of ITP.

In pubertant girls ITP often manifests itself (80%) as meno-metrorrhagia. Bleeding often results into anemia. Metroragia usually lasts from 2 to 4 weeks, it sometimes quite difficult to be stopped. Gastrointestinal haemorragies in patients can lead not only to anemia, but even to death (95).

Observations of patients with ITP showed that fragility tests capillaries are often positive because thrombocytes cannot perform their angiotrophic function (24). There is a decrease in the count of thrombocytes in the peripheral blood with normal or increased levels of plasma coagulation factors. The level of erythrocytes and hemoglobin may be normal. Post-hemorrhagic anemia is sometimes observed (23).

It was stated by the same author that the morphology of erythrocytes

depends on whether the patient had anemia and what its nature was. The degree of increase in the number of reticulocytes in the blood depends on the intensity of blood loss or hemolysis. The leukocyte count in most patients is normal or slightly

increased. Leukopenia occurs when two or three hematopoietic chains are impaired. In some patients, eosinophilia is detected, autoallergization here plays its role. There is an increase in the number of megacryocytes with a predominance of young forms in the bone marrow of most patients. But sometimes their number is within the normal range and only with exacerbation of the disease can sometimes be observed a temporary decrease in the number of megakaryocytes until their complete disappearance. Bleeding is often prolonged. Blood clot retraction is reduced. Blood coagulation is normal in most patients. Functional thrombocytes' disorders are often observed in case of autoimmune thrombocytopenia; their adhesion to glass decreases in some patients, platelets aggregation resulted from ADP, thrombin and collagens is impaired (17,35,55,147).

Thrombocytopenia is often accompanied by hereditary or congenital defects in the structure and function of thrombocytes, most often associated with insufficiency (inferiority) of enzymes or membranes. Bernard-Soulier syndrome is one of them. Giant forms of platelets, deviations in the activity of factor 3, the absence in the cytoplasmic membrane of megakaryocytes and platelets of glucocoprotein that interacts with WF (Willebrad's factor), VIII, V, XII blood coagulation factors as well as impairment of the ultrastructure of the membrane proved to be its symptoms. Duration of thrombocytes' existence is shortened while their production is preserved; that is why moderate thrombocytopenia with minor hemorrhages develops.

In hereditary, chromosome's X linked Wiskott-Aldrich syndrome, thrombocytopenia, on the contrary, is combined with microforms of platelets; the release reaction, aggregation ability, etc. are impaired. The number of megakaryocytes is normal or increased. Eczema, IgM and IgA deficiency, small T-lymphocyte deficiency, atypical plasma cells and extramedullary hematopoiesis, mainly in the lymph nodes and spleen proved to be another signs of the disease (96,175).

Severe thrombocytopenia (ampegakaryocytic thrombocytosis), rarely occurs in newborns, originates in case of hereditary megakaryocyte deficiency, combined with bilateral radial aplasia, renal or cardiac anomalies (11,67,173). Hereditary

thrombocytopenia with large thrombocytes is observed. This is the so-called “Family macrothrombocytopenia” form associated with a decrease in glucolyzed glucoprotein IV of thrombocyte’s membrane (17,37,97).

Developed thrombocytopenia may occur due to a decrease in the production of these cells (hypoplasia of hematopoiesis), increased destruction (under the influence of immune conflict or chemical compounds, including drugs), increased consumption of thrombocytes (DIC syndrome), mechanical injury to platelets, artificial circulation, etc. (93,113,139).

Developed thrombocytopenia is also observed in shock conditions, while thrombocytes are retained in the vessels of the abdominal cavity, i.e. a redistribution of the concentration of blood platelets is observed. In case of DIC syndrome, thrombocytopenia is associated with the destruction of thrombocytes by fibrin during the polymerization process and in the vascular wall due to their expressed aggregation and adhesion. In case of DIC syndrome in the decompensation phase, thrombocytes’ count reduces below the level of 100.0 x 109/l (38,67,110).

Thrombocytopenia is especially expressed in case of sepsis caused by gram-negative bacteria. In this case thrombocytes bind to endotoxins and antibodies, they are quickly eliminated from the bloodstream.

Thrombocytes’ consumption may occur during operations with

using an artificial blood circulation apparatus, the membranes of which are gradually covered with blood platelets. Severe thrombocytopenia can occur during hemodialysis as well as in case of usage heart-lungs devices. In the latter case, thrombocytes are deposited both in the oxygenator and in the extracorporeal blood flow system. When a patient is connected to the heart-lung apparatus for a prolonged period of time, hemorrhagic complications may occur due to secondary thrombocytopenia (85,124,129).

There is a report in the literature of post-transfusion transient thrombocytopenic purpura occurring a week after blood transfusion and lasting 20-25 days (38).

There is evidence that a marked decrease in thrombocytes' count is observed in 1/4 of all individuals tested for AIDS (174).

The reaction between thrombocytes and their eluates was found in 1 out of 10 examined homosexuals, whereas in case of AITP, accordingly, in 12 out of 15 patients. An increase in the level of the immune complex (IC) which interacts with thrombocytes was revealed in 88% of homosexuals and not a single patient with AITP. The IgG serum fraction in AIDS did not react with thrombocytes of healthy people while in case of AITP it reacted with intact blood platelets. It was noted that in case of AIDS thrombocytopenia is caused by the deposition of IR and complement on platelets, unlike AITP, in which class G anti-thrombocyte's antibodies are formed.

This fact indicates that thrombocytopenia may be one of the hidden symptoms of the development of AIDS.

H. G. Goodsweig et al. (1986) observed 25 homosexual men aged 27-47 years with thrombocytopenia, consistent with all clinical and laboratory indicators of AITP. Two of them developed AIDS with a fatal outcome, 8 people experienced spontaneous remission with normalization of the thrombocytes'count, 4 had no serious indications for therapy; 12 responded well to therapy with high doses of prednisone, 2 patients underwent splenectomy. Since thrombocytopenia is common in AIDS, the authors consider its occurrence in homosexuals as a prodromal symptom of this disease.

There is a special group of patients with thrombocytopenic symptoms that occur in certain diseases: B12-folate-deficient-polydeficiency anemia with thrombocytopenic symptom, thrombocytopenia with depression of hematopoiesis, thrombocytopenia with leukemia, thrombocytopenia with malignant lymphomas, thrombocytopenia with liver diseases, thrombocytopenia with systemic lupus erythematosus, rheumatoid polyarthritis, radiation disease.

It has been shown that one of the reliable symptoms of hemolytic anemia is an enlarged spleen (from slightly to severe splenomegaly). In most of these patients the thrombocytes' count remains normal or slightly decreased. However, a combination of autoimmune hemolytic anemia with severe thrombocytopenia is possible, or

simultaneous autoimmune impairment of all three germs is possible. In some cases autoimmune hemolytic anemia begins simultaneously with autoimmune thrombocytopenia, in others, thrombocytopenia occurs several months or years later. In some patients, thrombocytopenia is revealed at the onset of the disease and after a certain time anemia occurs, but thrombocytopenia may not be present (7,31,134,137).

The exceptional interest shown recently in the study of thrombocytes' hemostasis disorders is determined by the large role played by blood platelets in the pathogenesis of a number of diseases and conditions of the body accompanied by microcirculatory disorders or the occurrences of hemorrhages (109,120,139).

It is known that the development of bleeding syndrome is largely due to insufficiency of the blood platelet-megakaryocytic apparatus in case of chronic hepatic diseases. With the involvement of the spleen in the pathological process, all chains of the thrombocytes' hemostasis system are disrupted: the number of thrombocytes is reduced, their kinetics are disrupted and their adhesive-aggregation function is decreased (3,47,57,).

Sometimes patients with liver cirrhosis develop significant changes in the activity of the megakaryocyte apparatus, which is expressed, first of all, by a decrease in the number of thrombocytes in the peripheral blood by 2.25 times. In this case, the blood platelets are functionally suppressed, which is expressed in an extension of the moment of onset of aggregation by 2.6 times and a decrease in the degree by 1.27 times (57,93,134). In case of liver cirrhosis, uncomplicated by hypersplenism, the number of blood platelets decreases by 2.2 times, the life of thrombocytes is shortened by 1.4 times and daily thrombocytopoiesis decreases by 20.3%. A different picture is observed in patients with liver cirrhosis complicated by hypersplenism. Under these conditions functional activity decreases by 2.3 times against the background of a 2-fold decrease in the number of blood platelets.

The liver promotes the maturation of functionally valuable megakaryocytes, and after itsimpairment megakaryocytopenia and thrombocytopenia develop due to a violation of this function (4,24,112).

Hemorrhagic manifestations in case of chronic hepatitis and liver cirrhosis aggravate the disease, sharply reduce a person's ability to work and sometimes lead to death. Thrombocytopenia is manifested clinically by skin hemorrhages in the form of blue spots that occur in places of skin trauma after injections, bleeding from the mucous membranes of the gums, nose and gastrointestinal tract; hematuria and uterine bleeding are less common.

Some researchers (16,73,107) note that bleeding occurs due to the complexity of the pathogenetic process in case of chronic liver diseases and, at the same time, they point out four reasons for the development of hemorrhagic diathesis in these patients: these are bleedings that occur as a result of impaired absorption of the K coagulant, a decrease in the synthesis of factors bloodcoagulation, thrombocytopenia and bleeding from esophageal veins.

It has been described (47,134) that in case of hypersplenism, a manifested thrombocytopenia with maturation delay in the bone marrow occurs in cells, namely elements of the megakaryocyte series with

the increase in the content of immature megakaryocytes. As a result of these changes the development and formation of blood platelets is impaired both quantitatively and qualitatively.

Most authors consider the spleen to be an organ that produces autoantibodies to blood cells. There is an opinion (58, 93, 95) that the highest percentage of anti-thrombocytes' antibodies is found in the spleen.

The influence of anti-thrombocytes' antibodies on the functional activity of platelets has been approved (97,101). In patients with liver cirrhosis, not only a violation of the adhesive-aggregation function of platelets, but also, in some cases, a complete lack of response to the addition of ADP to thrombocytes was found (57,78,115).

Thrombocytopenia in patients with liver cirrhosis is explained by the depositing function of the spleen. This function is possible due to the peculiarities of blood circulation in the spleen. The cause of thrombocytopenia is also associated with

increased accumulation of sequestration and destruction of blood cells in the spleen as well as in the liver.

Plasma proteins (including fibrinogen), being adsorbed on the surface of functionally active thrombocytes, affect their electrical charge and largely determine the ability of blood platelets to undergo functional changes. With fibrinogenopenia, platelets lose the ability to undergo these changes (16, 77,177).

An impairment of the fibrinolysis process was found in patients with liver cirrhosis along with a decrease in the adhesive-aggregation function of platelets; degradation products of fibrin and fibrinogen were found in 51% and 1% of patients. There are patients with chronic diffuse liver disease in whom the number of platelets in the peripheral blood was normal, but in some of them the course of the disease was complicated by hemorrhagic diathesis in the form of increased bleeding of the mucous membranes, subcutaneous hemorrhages, etc. (16.73). Besides, manifested disturbances in the functional activity of blood platelets with normal levels of plasma coagulation factors and normal spleen sizes were determined.

Therefore, along with thrombocytopenia functional disorders of platelets are often detected in patients with chronic diffuse liver diseases which may serve as one of the reasons of the development of hemorrhagic syndrome in case of this pathology.

Thus, we can conclude that the reason of these diseases proved to be the impairment of the megakaryo-thrombocyte system.

Thus, we can conclude that the reason of these diseases has proven to be the impairment of the megakaryo-thrombocyte system.

Treatment of ITP still remains a difficult problem. Therapeutic methods depend on the stage of the disease. If measures to combat bleeding proved to be number one during a crisis, then the prevention of exacerbations of the disease and its complications becomes of great importance during remission.At present the following therapeutic methods are used in the treatment of ITP: treatment with glucocorticosteroids, splenectomy and the usage of immunosuppressive and immunostimulating drugs (15, 24, 140). In addition to the above-mentioned treatment methods, both local and general hemostatic drugs are used in order to stop bleeding

as well as vitamin therapy and transfusion of blood components if indicated (16, 76,140, 161).

There is an opinion that treatment always begins with prednisolone at an average dose of 1 mg/kg. In severe cases, this dose may be insufficient, then after 5-7 days it may become doubled. The therapeutic effect usually appears in the first days of treatment. First, the hemorrhagic syndrome disappears and then the number of thrombocytes begins to increase. The first “portions” of blood platelets are almost entirely used to “feed” the endothelium. Treatment continues until the full effect is achieved. Then the dosage is gradually reduces and administration of glucocorticosteroids slowly stops. In some cases, one such course can lead to a final cure. However, more often after the withdrawal of hormones or even when trying to reduce the dose, a recurrence occurs requiring a return to the original high doses of the drug (14,140,161).

Observations of recovery of patients with ITP in 64% of cases after corticosteroid therapy with an acute form of the disease in adults are described in the literature (52,78,160).

However, not all authors express their enthusiasm for the good results of corticosteroid therapy, especially in case of chronic ITP. According to some data, in 10% of patients there is no effect of glucocorticosteroid therapy at all (55). With a normal and unstable effect during treatment with glucocorticosteroids (usually after 3-4 weeks from the start of therapy), many clinicians (76,140,161) recommend performing a splenectomy.

Indications for splenectomy in ITP are decided in each case specifically, depending on the characteristics of the clinical course, the initial state of peripheral blood parameters and bone marrow hematopoiesis of the patient (82,134).

Splenectomy in 80% of patients with ITP results into complete recovery in those patients in whom corticosteroid hormones had a good but unstable effect in the past (76,78,134). There is evidence that splenectomy results into stable normalization of thrombocytes’ level and the disappearance of clinical manifestations of ITP in 75% of patients; but thrombocytopenia remains in 15.4% (62,161).

The greatest difficulties in therapeutic terms were presented by the group of patients with autoimmune thrombocytopenia, for whom even splenectomy did not provide prolonged improvement in their condition. At the same time, a return to corticosteroid drugs, according to many authors, is ineffective or gives a temporary rather than stable effect, even when using high doses of hormones (72,55,140). They believe that such patients are indicated for treatment with cytostatic agents and immunosuppressants in combination with glucocorticosteroid hormones. The effect of immunosuppressive chemotherapy occurs after 1.5-2 months, after which they recommend gradually hormones withdrawing. Imuran, cyclophosphamide, vincristine, etc. are recommended as immunodepressants. There are reports in the literature that vincristine has advantages over other immunosuppressants (14, 62). These advantages are as follows: when using vincristine (1.5-2 mg/m 1-2times a week), a rapid therapeutic effect develops after 2-3 injections. There is a higher clinical effectiveness of vincristine - 67% versus 57% and lower, in comparison with the use of other immunosuppressants - imuran, cyclophosphamide, etc.

Treatment with donor's thrombocytes with vinblastine is recommended in case of thrombocytopenia if splenectomy is ineffective. Under these conditions, thrombocytes are quickly destroyed by macrophages, and macrophages are selectively exposed to vinblastine, which disrupts their function and results into death (52,60).

There is evidence that vincristine increases the number of blood platelets, increases the adhesive-aggregation ability of the latter and has a more manifested and immunosuppressive effect compared to other immunosuppressants (60,76,137). However, it sometimes causes damage to the peripheral nervous system (polyneuritis, intestinal paresis).

The disadvantages of the used cytostatics (imuran, cyclophosphamide, etc.) include a high percentage of the likelihood of tumor transformation.

Observations g. Agnelli et ai (1982) demonstrated side effects in 44.4% of patients while using immunosuppressants. Besides, there are many controversial and controversial issues regarding the dose, duration of treatment, indications and

contraindications, especially in pregnant women and children (8,15,139). To increase the effectiveness of immunosuppressants, it is necessary select individually these drugs based on their effect on the interaction of T- and B- lymphocytes with an antigen or antigen-antibody complex (119, 51,34, 74, 103). However, as the authors pointed out, immunosuppressive therapy causes depression of the immunocompetent system with a sharp decrease in the number of mature T- and B- lymphocytes and an increase in “zero”- lymphocytes devoid of T- and B- lymphocyte markers; so they believe that treatment only with immunosuppressants, despite clinical effectiveness does not provide correction of the impaired immunocompetent system, this poses a significant danger in terms of further prognosis of the disease, the addition of secondary infections and the occurrence of malignant neoplasms against the background of suppressed immunity. Therefore, the above-mentiones and a number of other authors recommend the use of immunostimulating therapy with drugs such as thymosin, anti-T-lymphocyte gamma globulin, low doses of decaris, sodium nucleinate and T-activin (58, 70, 129, 161).The authors provide data that in the process of immunocorrective therapy an increase in the reduced content of T-, Tj-lymphocytes occurs and, conversely, a decrease in the increased population of B- and “zero” lymphocytes, normalization of membranes due to improved phagocyte function is observed.

V.N. Shabalin, L.D. Serova (82) studied the therapeutic effectiveness of antilymphocyte globulin (ATG) in 26 patients with autoimmune thrombocytopenic purpura (AITP). The duration of the disease ranged from 1 to 20 years (chronic form of the disease). Also the authors relied on the assumptions of a deficiency of suppressor cells, the selectivity of the action of ATG on the T-lymphocyte population, and the immunostimulating effect in using small doses of the drug (0.7-0.8 mg/kg). The drug was administered intravenously in 150 ml of saline, 7-10 infusions at 24-hour intervals against the background of symptomatic and steroid therapy. It was found out that hemorrhagic phenomena disappeared in 19 patients, decreased to a mild degree in 6, ineffective treatment was observed in 1 patient after the complex treatment. Immunological investigations showed that after treatment

there was a moderate decrease in the number of T-lymphocytes, a significant decrease in B-lymphocytes and the level of T-cells increased significantly. After the complete course of ATG therapy, the thrombocytes' count increased from 10-20x109/l to normal within 2-4 months in 12 of 26 patients. No significant positive changes were revealed in 10 out of 26 patients according to clinical and laboratory data.

It is believed that the principle of immunocorrective therapy for patients with AITP is the combined use of immunosuppressants to suppress the increased function of B-lymphocytes and selective immunostimulants to increase the reduced function of T-cells (58,133).

It is considered that there is a large amount of IgG of various classes on the surface of thrombocytes of patients with AITP. These Igs are:

a) antibodies against thrombocyte's antigen;

b) antibodies against allogenic thrombocyt's antigens formed during blood transfusion, blood platelet mass or pregnancy;

c) antibodies against autologous or heterologous antigens,
adsorbed on thrombocytes;

d) immune complexes formed from those attached to
immunoglobulin receptors of platelets C3 and CI-components
complement.

Patient's blood platelets destruction can be carried out due to antibodies directed against thrombocytes and due to the activation of complement with subsequent phagocytosis of platelets by Ig RES cells (37,93). Immunoglobulins can bind not only to thrombocytes, but also to megakaryocytes. It is possible that Ig fixation on megakaryocytes during AITP changes the properties of the membrane and disrupts the process of platelet formation (75).

In connection with the above, there was an assumption that Ig could be used to treat

AITP. This opinion of the authors is based on the fact that under the influence of Ig the formation of antibodies directed against thrombocytes is prevented. Numerous observations carried out in recent years have shown that the administration

of Ig at a dose of 150-500 mg per 1 kg of kg body weight during 5 days often eliminates the main symptoms of the disease. The best effect is obtained with intramuscular administration, since in the

The effect of high doses of monomeric IgG on the course of AITP was studied in 8 children with different periods of the disease (103). It was noted that the clinical effect manifests itself after the first infusion; tissue bleeding decreases, hemorrhagic syndrome gradually disappears. A significant increase in the number of platelets was observed in 5 out of 8 children after the second injection. In 3 children no increase in thrombocytes' count was observed, although a manifested clinical effect was noted. The authors consider that high-dose IgG therapy can be used to obtain a rapid hemostatic effect, for example, during various surgical interventions.

The mechanism of the therapeutic effect of IgG in AITP is not fully cleared. It was established that the administration of IgG reduces the concentration of immune complex, therefore reducing thrombocytes' phagocytosis (156). According to the author, large doses of Ig G probably interfere with the production of antibodies against blood platelets.

B. Gross et at (188), studying various IgG preparations, came to the conclusion that the therapeutic effect in AITP occurs only if IgG in high concentrations binds directly to thrombocytes. The authors put forward the following hypotheses for the therapeutic effect of IgG:

1. High concentrations of monomeric Ig create protective barrier on thrombocytes from the action of antibodies.

2. Monomeric Ig pre-binds complement-fixing and cytotoxic IgG aggregates, preventing their fixation on the surface of thrombocytes.

3. Monomeric IgG protects platelets from activation of immune complexes.

4. A high level of monomeric IgG "envelops" the Fc receptors of mononuclear cells and, thereby, prevents thrombocyte's phagocytosis.

In recent years to relieve thrombocytopenic crisis it is recommended to use intravenous human immunoglobulin (165). The first report on the effectiveness of immunoglobulin treatment was made by clinicians (190), who treated 13 sick

children with acute and chronic forms of the disease. The drug was administered intravenously in the dosage of 0.4 g/kg for 5 days. In all patients, the number of thrombocytes increased within 1-2 days to 150.0x10 9/l - 600.0x10 9/l. A particularly manifested effect was noted in the treatment of acute forms of the disease.

An increased fibrinolytic activity of the blood is observed in patients with ITP due to the decrease in the number of thrombocytes. Therefore, some authors (12, 108, 132) recommend the use of E-AKK as a means of reducing the fibrinolytic activity of the blood. Clinical improvement can be achieved (cessation of bleeding, disappearance of petechial rash, resorption of ecchymoses) after management of E-AKC. Researchers have not noted any increase in thrombocytes during treatment with E-ACC (84, 108, 154) and, at the same time, E-ACC can cause undesirable reactions. In cases of severe anemic syndromes transfer single-group red blood cells can be recommended(12, 23, 127). Thus, the search for more effective drugs for the treatment of ITP proved to be topical.

Impaired hemostasis due to thrombocytopenia and acquired qualitative thrombocytes' deficiency is best corrected in the process of adequate treatment of the underlying disease, which, however, is often difficult to treat.

Hemostatic agents play a significant role in the complex therapy of diseases complicated by hemorrhagic syndrome. Red blood cells, native plasma and platelet suspension proved to be the most effective ones. There is an opinion that the therapeutic effect of concentrated platelet mass is associated with the introduction of lamellar factors and serotonin into the patient's bloodstream, which results into the improvement in the blood coagulation system and the increase in the resistance of blood vessel tone (25,156). We should keep in mind that transfusion of platelets without taking into consideration the blood group and Rh factor contributes to the sensitization of patients and reduces the effectiveness of subsequent thrombocytes' transfusions.

It was observed by other clinicians that transfusion preserved blood does not have a manifested hemostatic effect (29,60,74). A positive effect is observed only when using fresh citrated blood, especially with direct transfusions. It is necessary to

use blood from the earliest storage period (up to 48 hours) for the treatment of thrombocytopenic bleeding. In addition, according to some authors, the effect of blood transfusions in patients with thrombocytopathy is short-termed, it is associated with the destruction of donor's thrombocytes.

Another group of drugs that can inhibit fibrinolysis belongs to proteolytic enzyme inhibitors (trasylol, contrical, inicrol, etc.). They inhibit the activation of profibrinolysin and fibrinolysin.

Erythrophosphatide, lipomyase fat emulsion, erythromycin and other drugs with high thromboplastic activity are successfully used for hemorrhage caused by thrombocytopenia (25,156). These drugs normalize the time of recalcification, increase the consumption of prothrombin, and the activity of the fibrin-stabilizing factor.

Drugs that improve blood platelet function have an effect When the adhesive-aggregative function of thrombocytes is inhibited are the following: synthetic progestins, ATP, magnesium oxide, lithium carbonate, prostaglandins (17,24, 140).

Adrenaline preparations (adroxan, divaxan), serotonin have a wide spectrum of action. They increase the resistance of the vascular wall and enhance the adhesive-aggregation function of thrombocytes(140).

The drug dicinone has a broad hemostatic effect. It improves thrombocytes' function and reduces capillary permeability (140). Dicynone acts as a catalyst for enzymatic reactions in the area around the thrombocutes' circumference as well as in the vascular endothelium.

Experimental data are presented indicating that after 2 hours a significant activation of the platelet component of hemostasis develops as a result of a single administration of prednisolone in the dosage of 0.5 mg/kg: the number of platelets in the peripheral blood increases, the ability of platelets to adhesion-aggregation increases. However, a month later, a decrease in the functional activity of platelets was observed against the background of a sharp suppression of glucocorticoid function of the adrenal glands. An opinion has been expressed that dystrophic changes in the adrenal cortex and depletion of its functionality in patients with severe

hemorrhagic syndrome result into a decrease in the ability of the blood coagulation system to provide hemostasis. The beneficial effect obtained with the help of glucocorticoids in thrombocytopenic bleeding was explained mainly by a decrease in vascular permeability; also in case of immune thrombocytopenia the inhibition of the effect of hormones on the processes of immunogenesis proved to be significant (7,21,161).

Along with drugs of chemical synthesis herbal preparations are used to treat patients with ITP and thrombocytopenia of various origins, since they do not cause side effects, have a multifaceted effect on the body and can be prescribed for a long time.

A thrombocytes'-stimulating effect of caperza root tincture has been revealed (34). A scheme for the effective treatment of patients with congenital and acquired forms of blood platelet disorders with infusions of plantain, nettle and yarrow leaves has been developed (2,154).

Summarizing the above literature data, we can conclude that the drugs used for thrombocytopenia of various origins are ineffective and expensive; their usage is fraught with side complications, so the search for effective, specific drugs that stimulate thrombocytopoiesis remains topical.

I. 3. Preparations of barberry vulgaris in the clinic of internal diseases

The healing properties of barberry have been known since ancient times. The Babylonians and Hindus used barberry berries as a blood purifier (650 BC).

The great thinker Abu Ali Ibn Sina (Avicenna) writes that barberry berries (zirik or cupid boris) are red and round in the valleys, black and oblong in the sands or mountains. They "strongly drive bile in the form of tea" strengthen the liver, stomach and quench thirst well, strengthen and help against ulceration of the intestines. The root helps against "bleeding" from the lower parts of the body. In the form of a medicinal bandage it helps against hot "tumors". As indicated in "Al vohiya" by Abu Ali Ibn Sina, barberry (anorboris) strengthens the heart, liver, stomach, and is an antipyretic, antiemetic, and appetite stimulant. According to the

information given in the book of Sayyid Subkhonkuli Muhammad Bakhodurkhon “Ekh-ut-tibbi Subkhoni”, food to which barberry fruits are added is beneficial for jaundice. As indicated in “Makhzun-ulaudwiya” by Muhammad-Khusayin, barberry eliminates bile, strengthens the stomach, strengthens the heart, slows down the excited strong flow of blood and is useful for hemorrhoids. In combination with cinnamon, honey and other spices, it cures dropsy and is also used to open liver blockages (4).

The use and study of plants of the Berberidaceae family are associated with the presence of the alkaloid berberine, which is found in the roots, stems and leaves. The berberine content in various types of barberry ranges from 1.5 to 9%. The main source is Berberis Vulgaris, in which about 1-2% of the alkaloid is determined. Berberine is isolated in small quantities from plants of the family Rameneulaceae-Caltha palustrish, Papaveraceae (Chelidonium majush) and various species of corydalis. The content of berberine in plants of different types of barberry growing at different altitudes varies over a fairly wide range, and a decrease in the amount of berberine is observed as the plants rise to higher mountain place.

Nowadays, more than 20 alkaloids have been isolated from the studied species of the genus Berberis L; berberine, berberubine, palmetine, dihydrocordiamine, columbia, lambertine, epiberberine, iatrorecin, hydrostin, berbamunine, isotetranine, obaberine, obamegin, oxyacanthin, berbamin, chymatin, bervulcin, magnoflorin (33,45) as well as sugars, tannins and ascorbic acid.

The Pharmaceutical Committee of the USSR Ministry of Health has allowed

the usage of 20% tincture of Amur barberry leaves, and in 1955 - an aqueous infusion of common barberry leaves as a remedy for uterine bleeding associated with inflammatory processes. In 1957 the usage of tincture from the leaves of barberry was allowed as the remedy for liver diseases as well as the drug cholelitin for the treatment of cholelithiasis, cholecystitis and recurrent jaundice. This drug contains a tincture of barberry leaves and roots.

Since 1962 in practical medicine berberine sulfate, isolated from barberry was used as a choleretic drug (61).

Common barberry has several popular names: barberry-kislich, barberry, gorushka, sour tree, kvasnitsa, mokrisch, svaybaris. This is a bush 1.5-3 m high. The shoots are smooth, ribbed or furrowed, the trunks and shoots have numerous three or five separate thorns. The leaves are elliptic, elongated, ovate,

wedge-shaped, narrowed into a short petiole, obtuse or pointed, evenly toothed along the edges, ciliated and finely serrated, sometimes almost the entire part. The inflorescences are simple, the racemes are drooping. The flowers are six-membered with a double perianth. It blossoms in May-June. The fruits are juicy, oblong, berry-shaped, the single leaf is brown or dark red in color with a slight waxy coating. The seeds are dark brown, ovoid, the fruits ripen in July and August. Grows in floodplains of rivers, on the slopes of terraces above the floodplain.

Literature analysis data on the usage of berberine alkaloid in modern biology and medicine indicated that it proved to be one of the most used natural alkaloids. Berberine had not yet been obtained synthetically, but was widely used in development to create products for the chemical modification of its molecules. Interest in berberine was due to the high ability of different forms of the alkaloid, the reliability of methods for its isolation, analysis and identification as well as its prevalence in plants of various families and the availability of large reserves of raw materials.

The main biological properties include choleretic and antimicrobial effects. No less remarkable is the general biological feature of the alkaloid, such as the ability to bind to carriers of hereditary information - the DNA of animal cells. A numerous list of dosage forms of barberry-based prescriptions used in modern scientific and alternative medicine testifies to the great popularity of this plant. At the same time the experience of herbal medicine from European, Chinese, Tibetan and Indian medicine testifies to the inexhaustible possibilities of complex herbal medicine. Therefore, it is highly desirable to try to use barberry and its preparations more widely in multicomponent complexes of effective, wide-spectrum agents actions. When studying experimentally in anesthetized cats, the alkaloid at a dose of 0.1-0.2 mg/kg results into a decrease in blood pressure by 25-30% and a slight increase in

respiration. At these doses, the drug has a weak inhibitory effect on the autonomic ganglia and enhances the contraction of the smooth muscles of the uterus and intestines. Berberine has some anticholinesterase properties and a depressant effect on the central nervous system, but does not exhibit an anxiolytic, anticonvulsant or analgesic effect.

Berberine has an antitumor effect, however, it does not increase the life expectancy of animals. The alkaloid has a bacteriostatic effect, increases the phagocytic activity of leukocytes and prevents the death of animals from septicemia, and is effective in patients with the initial stage of pulpitis. Berberine at a dose of 25 mg/kg and higher when administered orally prevents the death of young rabbits infected with cholera, provided that it is used early in in vitro experiments, berberine has a bactericidal effect against Vibrio cholerae, which is associated with inhibition of RNA synthesis in bacteria (41,51).

The drug is used in the treatment of chronic cholecystitis (34, 36). Berberine is prescribed in a dose of 5-10 mg 3 times a day for 3-4 weeks. As a result of treatment most patients experience reduction in pain in the right hypochondrium and dyspeptic disorders. The drug is available in tablets of 0.005 g (5 mg).

In medical practice leaves, bark, and roots of two types of plants are used: Amur barberry (B. amurensis Ruph) and common barberry (B. Vulgaris L). Along with these species, different-leged barberry is used (Medicinal Plants in the USSR, 1967). The roots are harvested during the dormant period of plants in spring (April) or autumn (October, November). The raw materials are dried in attics or under sheds with good ventilation, spread in a thin layer (up to 5-7 cm) on fabric or paper. The bark is harvested during the period of sap flow (April, May), when it is easily removed; it is dried in the same way as the roots.

In experiments on the study of barberry oblonga and barberry coin, T.Z. Zhumaboev (39) found that berberine chloride, an amount of alkaloids and herbal preparations when administered single or multiple times to dogs, causes an increase in the number of platelets by an average of 30-50%.

The chemistry of berberine and alkaloids of the plant of the genus Berberis L are devoted to the work of A. Karimov (45), who isolated more than 30 new alkaloids from them. The isolated alkaloids belong to 5 types of isoquinoline alkaloids. These studies are being conducted to find new sources of raw materials for the production of berberine and other types of alkaloid. He found that different organs of these plants have different types of isoquinoline alkaloids.

A study of the dynamics of alkaloid accumulation in leaves, stems and roots showed that the amount of alkaloids in roots increases by the end of the growing season and decreases in young shoots and leaves. During the period of mass flowering the amount of alkaloids in leaves and young shoots reaches 0.39% and 1.40%, respectively. However, in all periods of the growing season the total amount in the roots is always greater than in the above-ground part of the plant.

In medical practice, berberine is used for chronic hepatitis, hepatocholecystitis, cholelithiasis. Deserve attention to work indicating the cytostatic, antibacterial and heparin antagonistic effects of berberine sulfate and chloride. Berberine has anticancer blood cell inhibitory activity (34, 36).

Barberry tincture is used in obstetric and gynecological practice for atonic bleeding in the postpartum period for bleeding associated with inflammatory processes, etc. The tincture is taken 30 drops 3 times a day for 2-3 weeks.

As a choleretic agent, berberine bisulfate is prescribed in tablets of 0.005-0.01 g 3 times a day before meals. Barberry bark is included as a “cholelithin”, used in the treatment of liver and gallbladder diseases.

Barberry roots are part of the Zdrenko’s mixture, used in the treatment of malignant tumors.

An extract from the roots is successfully used to rinse sore gums and sometimes in the treatment of eczema. To do this, prepare an infusion: half a teaspoon of crushed bark or root per glass of boiling water and drink 0.5 cups 3-4 times a day before meals.

In foreign medical practice, barberry preparations are used in the treatment of gastric and duodenal ulcers as a hemostatic and choleretic agent.

V.P. Bazaron., T.A. Aseeva (14) demonstrated that berberine is effective in the treatment of leishmaniasis. Barberry fruits are used as a source of vitamin “C” for hypovitaminosis conditions; various drinks, jams, etc. are prepared from it.

The presented literature data indicate that the barberry preparation has not been subjected to special studies aimed at studying its effect on thrombocytopoiesis which is the focus of the present work.

CHAPTER II. MATERIALS AND RESEARCH METHODS

II.1. General characteristics of experimental studies

Experiments have been carried out under conditions of a chronic experiment To study preparations of barberry vulgaris as thrombocytopoiesis stimulator, as well as to transcript the mechanism of their action on the megakaryocytic-platelet system of intact rats, on 230 mature outbred white rats of both sexes weighing 160-200 g.
The experimental animals were kept on a regular diet in vivarium conditions of the institute.

Studying drugs, administration and doses are presented in Table I.

Table I

№	Name of drug	Administration	Dose
1	Barberine bisulfate	Intraperitoneally once	1 ml / 100 g
2	Decoction of barberry vulgaris root	Intraperitoneally once	1 ml of decoction per 100 g of animal weight
3	Physiological solution (control)	Intraperitoneally once	1 ml / 100 g
4	Yarrow infusion	Intraperitoneally once	0,1 ml / 100 g
5	Donor's serum	Intraperitoneally	1 ml / 100 g

Experimental studies have been carried out in the following areas:

1. Study of the effect of barberry vulgaris preparations (berberine bisulfate and barberry root decoction) on the thrombocyte count in peripheral blood in intact rats. The results of the study were compared with the effect of yarrow infusion (taken as a standard) and 0.9% (physiological) sodium chloride solution (control) on the number of platelets in the peripheral blood of rats. 4 groups of experimental animals (40 rats) have been used in the experiment.

The studies were carried out before the administration of drugs (initial data) and after 1, 3, 6, 10 days after the administration of the proper drug.

2. The study of the effect of barberry vulgaris on the number of rat bone marrow megakaryocytes. To resolve this issue, we carried out experiments on 90 rats, which were divided into three groups 30 rats in every one:

I. group - animals were injected with a solution of berberine bisulfate,
II. group - animals were injected with decoction of barberry vulgaris root,
III. group - animals were injected with sodium chloride solution (control).

The studies of bone marrow were carried out before the administration of drugs (initial data) and after 1, 3, 6, 10 days after the administration of the proper drug.

3. Study of the thrombocytopoietic activity of the blood serum of donor rats (after drug administration). Thrombocytopoietic activity was assessed by the severity of the increase in the number of platelets in the peripheral blood of recipient rats caused by the introduction donor blood serum. For this purpose, the serum of donor rats' blood was obtained before the platelet reaction after the administration preparations of berberine bisulfate and decoction of barberry vulgaris root; that is on the 5th day after the administration of the corresponding drug, blood was taken and serum was separated. Serum was administered to recipient rats once, intraperitoneally. Studies were carried out before the administration of blood serum (initial data) and 1, 3, 6, 10 days after the administration of serum. Animals injected with saline sodium chloride

served as control group. These studies were carried out on 60 rats, which were also divided into 3 groups.

4. The presence of thrombocytopoietic effect of the blood serum of patients received the preparations of barberry vulgaris by biological method of study. In patients-donors, blood serum was obtained twice. The first portion of serum was received before the treatment of patients with thrombocytopenia with berberine bisulfate or barberry root decoction, the second portion on the 5th day from the start of treatment with these drugs. Recipient rats were initially injected once, intraperitoneally, with the first portion of serum; then, after 6 days, a second portion of the serum.

Studies were carried out on I, 3, 6 days after the first administration of serum and studies were continued on I, 3, 6 and 10 days after the administration of the second portion of serum. The results of the study obtained at the specified time from animals that were injected with the blood serum of healthy people and physiological sodium chloride solution were the controls in this series of experiments. 4 groups of experimental animals (40 rats) were used.

II.2. Methods of study of thrombocytopoiesis state in experimental animals (rats).

Blood for counting platelets was taken by cutting the end of the tail in rats. To count the number of platelets, the tube method was used; 0.02 ml of capillary blood was placed in a test tube with 4 ml of Peters solution. The number of platelets was counted in a Goryaev chamber under a microscope with a phase-contrast attachment (PC).

The state of the megakaryocyte bloodline of hematopoiesis was assessed by examining bone marrow punctures. Bone marrow collection from rats was carried out as follows: the rats were killed by decapitation, then the femurs were quickly removed, cleaned of adjacent muscles, and the epiphyses were cut off from both sides.

Bone marrow was washed out of the femur with 1 ml of warm (37°C) 0.9% sodium citrate solution (hypotonic solution) and placed on a paraffin-coated watch glass. The bone marrow was thoroughly mixed with a glass rod; 0.5 ml was taken into an erythrocyte melanger, dissolved the erythrocytes to the 101 point, then a 5% solution of acetic acid was taken. The absolute number of megakaryocytes from this part of the bone marrow punctate was calculated in the Fuchs-Rosenthal chamber.

From another part of the bone marrow punctate remaining on the glass, smears were prepared, dried, fixed and stained according to Leishman. 100 elements were counted in the smears: megakaryoblasts, basophilic polychromatophilic, oxyphilic, involuting megakaryocytes, isolating functioning megakaryocytes, as well as free nuclei, and displaying a portional megakaryocytogram. The absolute number of megakaryocytes was counted in a Fuchs-Rosenthal chamber. Thrombocytopoietic activity of the serum of donor animals was assessed according the severity of stimulation of thrombocytopoiesis by the administration of donor serum to recipient rats.

The experiments were carried out on 60 rats, which were divided into 3 groups 20 rats in each one. In animals of the first group, thrombocytopoiesis was stimulated with a single intraperitoneal injection of drugs (berberine bisulfate or decoction of barberry vulgaris root) in the dose of 1 ml/100g. To obtain serum, blood was extracted by cardiac puncture and then centrifuged at 1500 rpm for 30 minutes.

Animals of the second group were injected with 1 ml/100 grams of body weight of serum obtained from rats of the first group on the eve of the platelet reaction (the fifth day after drug administration), using a similar method.

Animals that were injected with physiological sodium chloride solution had been used as a control group (group 3).

II.3. General characteristics of clinical studies

Clinical studies of barberry vulgaris preparations were carried out on 130 patients; from them 67 patients were with ITP, 52 patients had anemia with symptomatic thrombocytopenia, 30 patients had hematopoietic depression, 16 patients with malignant lymphoma, 15 patients had liver disease with symptomatic thrombocytopenia. The control group consisted of 40 patients; from them 10 patients had ITP, 10 patients had anemia with symptomatic thrombocytopenia, 6 had leukemia, 10 had malignant lymphoma (Table 2).

Observations were carried out in the hematology departments of the clinics of Andijan State Medical Institute, the 1st Andijan Regional Children's Hospital and medical radiology of Scientific Center of Russian Academy of Medical Sciences (Obninsk).

Patients were prescribed the drug berberine bisulfate 5 mg 3 times a day 30 minutes before meals for 15 days. A decoction of barberry root was given before meals. 50 grams of dry barberry root boiled in 1000 ml of distilled water for 20 minutes, settled and then filtered. The decoction was given to patients 1 tablespoon 3 times a day 30 minutes before meals for 15 days. Blood for research from patients was taken from the fourth finger before administration of the drug 5, 10, 15 days from the start of the course of treatment 1, 2, 3 months after the end of the course of treatment.

The number of platelets in the peripheral blood, the adhesive-aggregation function of platelets, the time of primary bleeding, the time of blood clotting (capillary), the thrombocytogram was studied, a biological test was carried out to study the thrombocytopoietic activity of the blood serum of patients during treatment with berberine bisulfate preparations and a decoction of barberry root. Blood serum was used to carry out biological test (see 2.1).

II.4. Methods of study of the thrombocytopoiesis state in patients

Patients with ITP composed 67 people or 87% of the total number of patients who received treatment with barberry preparations. Among them there were women

(67%) and 22 men (33%). As it can be seen from Table 2, the majority of patients were persons of both sexes aged from 15 to 24.

In diagnosing ITP, such conditions as presence of thrombocytopenia, prolongation of the primary bleeding time, changes in the adhesive-aggregation function of blood platelets and absence of a primary disease that could cause thrombocytopenia had been taken into consideration. Microcirculatory type of bleeding mostly nose bleeding in 26 patients, bleeding from gums in 17 patients, hemorrhagic manifestations in 10 patients in the form of skin extravasation and in 13 sick women hemorrhagic syndrome manifested itself in the form of heavy bleeding from uterus, i.e. menstruation characterized by a long cycle had been observed in patients with ITP during investigation.

Based on the above mentioned signs, we divided the severity of bleeding into 3 degrees: mild, moderate and severe.

For a mild degree, a characteristic sign was the appearance of single ecchymosis and petechiae on the skin after external influences, nose bleedings.

For moderate severity, the appearance of skin extravasation and frequent bleeding were observed which appeared spontaneously under the influence of unfavorable exogenous factors. Postoperative bleeding was often observed; women usually had metrorrhagia.

Manifestation of hemorrhagic syndrome complications (post hemorrhagic anemia) in combination with various bleedings had been the criteria for severe degree.

All studied patients with ITP had been divided into the following groups according to the used therapy and its effectiveness.

Group 1 included 23 patients with mild to moderate severity of the disease, whose blood platelet count averaged 101,0x 109/l.

Group 2 included 24 patients with mild to moderate severity of the disease, whose blood platelet count averaged 110.0x109/l.

Group 3 included 14 patients with severe disease. Their average blood platelet count was 81,0x109/l. This group included those patients who had severe

hemorrhagic syndrome; severe anemia resulted from frequent bleeding of various locations. Administration of only barberry preparations did not increase the number of blood platelets in the peripheral blood and therefore patients were intravenously infused thrombomass, erythrocyte mass, E-ACC, glucocorticosteroid therapy was administered, and hemostatic and vasoconstrictor drugs were prescribed.

Group 4 (control) included 10 patients with ITP of different degree of severity. This group received treatment using traditional methods without barberry preparations: prednisolone therapy, intravenous administration of single-group thrombomass, erythrocyte mass, E-ACC, etc. The platelet count in these patients averaged 105,0x 10 9/l.

According to the duration of the disease, all patients with ITP were divided into 2 groups; Group I - 50 patients with a chronic course, Group 2 - 17 patients with an acute course.

Clinical and hematological characteristics of patients with anemia accompanied by symptomatic thrombocytopenia.

52 patients with anemia and symptomatic thrombocytopenia were under our supervision and from them 19 were treated for polydeficient anemia, which composed 10.5% of the total number of examined patients; among them 14 were women (74%), 5 were men (26%). It should be noted that in this group the number of sick women was 3 times higher than the number of men. The history of anemia was more than 5 years.

From 19 patients with polydeficient anemia only in 10 patients hemorrhagic syndrome was observed, in 2 patients - skin extravasations, in 2 patients gums bleeding, in 6 female patients with metrorrhagia. In addition to etiopathogenetic therapy patients took the preparation of berberine bisulfate. Control group of patients with polydeficiency anemia (10) and symptomatic thrombocytopenia received only vitamins B, C, folic acid and iron supplements treatment.

33 patients were under observation for hemolytic anemia and symptomatic thrombocytopenia (18.3%); among them 7 men (23%) and 26 women (77%), 2 patients were observed for acquired hemolytic anemia, 30 patients for hereditary

hemolytic anemia (B-thalassemia minor), 1 – a patient with hereditary hemolytic anemia of Minkow-Shaffar. Hemorrhagic syndrome in these patients was characterized by: in 6 patients - in the form of nosebleedings, in 11patients - skin extravasation, in 4 patients - bleeding from the gums, metrorrhagia - in 3 women.

Thrombocytonenia did not develop immediately in the observed patients with hereditary hemolytic anemia. For example, patient K.D., born in 1964, has been ill since childhood; bleeding from nose and gums, as well as heavy and prolonged menstruation have been appeared in recent years.

In some patients with hereditary hemolytic anemia, although thrombocytopenic symptoms were observed, bleeding was not noted. For example, patient D.U., born in 1966, has been ill since childhood; the decrease of blood platelet count observed over the past 2 years was not accompanied by bleeding.

These patients were divided into 2 groups: group 1 (20 patients) took the drug berberine bisulfate, group 2 (13 patients) took a decoction of barberry vulgaris root. Patients with hemolytic anemia took barberry vulgaris preparations along with other drugs, such as prednisolone, detoxification drugs; patients with severe anemia were given intravenous infusions of washed red blood cells, vitamin therapy, etc.

II.5. Clinical and hematological characteristics of patients with hematopoietic depression.

We observed 13 patients with hypoplastic anemia (7.2%), some of the patients in this group (7 patients) took berberine bisulfate simultaneously with other drugs: iron supplements, vitamins, prednisolone, intravenous infusion of red blood cells, etc. Another part (6 patients) took a decoction of barberry root without other medications in an outpatient department. In this group of patients, hemorrhagic manifestations were observed in two or three manifestations, that is, one patient simultaneously experienced nasal and gingival bleeding, as well as petechial rashes on the skin.

All patients had a chronic course, including two patients who were admitted after splenectomy. All examined patients had severe thrombocytopenia upon admission to the clinic (platelet count ranged from $30,0x10^9$/l to $80,0x10^9$/l).

17 patients with leukemia (9.1%) have been examined as well. This group included 9 women (57%), 8 men (47%) aged from 15 to 60 years. Among them there were 11 patients with acute leukemia (this group included 9 patients with acute undifferentiated leukemia, 1 patient with acute lymphoblastic leukemia, 1 patient with acute myeloblastic leukemia). Patients with chronic leukemia - 6; among them 2 patients were with chronic lymphocytic leukemia, terminal stage, 4 patients were with chronic myeloid leukemia in the terminal stage.

On admission to the hospital in 13 patients the blood platelet content in the peripheral blood was in the range of 100,0x10 ^{9}/l – 170,0 x10 ^{9}/l. Severe thrombocytopenia was observed (blood platelet count 60,0x 10 ^{9}/l - 80,0x10 ^{9}/l) in 4 patients during hospitalization.

Patients were prescribed berberine bisulfate simultaneously with cytostatic drugs in courses of VAMP (vincristium, ametoptyrine, 6-mercaptopurine, prednisolone), CVAMP (cyclophosphamide, vincristine, ametoptyrine, 6-mercaptopurine, prednisolone) therapy.

The control group consisted from 6 patients with leukemia, who received treatment with cytostatic drugs without taking berberine bisulfate. The average thrombocytes count was116,0 x10 $^{9/}$l.

Patients with malignant lymphomas (16 patients); from them 13 patients with lymphogranulomatosis, 3 patients with lymphosarcoma have been examined. The control group of patients consisted from 14 patients who did not receive berberine bisulfate; from them 10 patients with lymphogranulomatosis, 4 patients with lymphosarcoma. The age of the patients ranged from 16 to 61 years, men - 15, women - 15. In this group of patients, thrombocytopenia occurred after a course of polychemotherapy in combination with radiation.

15 (8.5%) people were the patients with liver disease. From them 13 patients with liver cirrhosis, 6 patients with splenomegalic liver cirrhosis, 4 patients with portal cirrhosis, 2 patients with chronic active hepatitis, 3 patients after viral hepatitis condition.

Hemorrhagic syndromes were noted in the observed patients: in 2 patients in the form of nosebleedings, in 4 patients - skin extravasation, in 2 patients - gums bleeding, in 1 patients – metrorrhagia, in 1 patient - gastrointestinal bleeding.

One group of patients (10 patients) received the drug in the hospital in the form of berberine bisulfate tablets; another group of patients took the drug in an outpatient department in the form of barberry vulgaris root decoction.

II.6. Methods of thrombocytopoiesis study in patients.

The rate of capillary blood coagulation was determined according to the method of Sukharev (1983). The start of coagulation using this method normally ranges from 30 seconds to 2 minutes, the end of coagulation is from 3 to 5 minutes. Blood from a 4th finger of the patient's hand is taken and drawn into a capillary tube (the height of the blood column is 25-30mm). The time of blood taking is noted using a stopwatch, and the blood is transferred to the middle of the tube by tilting the capillary. Holding the capillary with two fingers, rock it, tilting it 30-45° in both directions. Free movement of blood indicates that blood clotting has not yet begun. The onset of blood clotting is characterized by a slowdown in blood movement when the capillary is tilted. Small clots appear on its inner wall. Complete blood clotting corresponds to the moment when blood movement in the capillary completely stops.

Adhesion and aggregation of platelets was studied according to the method of S.I. Chekalina and O.Yu. Tokarev (1983). This method is as follows: after treating the finger with alcohol, a puncture is made with a depth of 3-4 mm. In a siliconized micropipette containing 0.04 ml of 3.8 % sodium citrate solution, draw 0.2 ml of blood (to the top mark) and carefully blow the contents of the pipette into the bottom of a siliconized test tube. Take another 0.2 ml of blood freely flowing from the puncture into the same test tube and blow it into the same test tube. Easy mix both portions with air blown from a pipette, then 0.2 ml of citrate blood is drawn into the same pipette and transferred into a non-siliconized microtube.

Both test tubes are placed in a rack installed in the center of the switched on electromagnetic stirrer. A metal rod coated with plastic is lowered into a siliconized microtube; in 20-30 seconds into the melanger for counting red blood cells blood is drawn from this test tube to the 0.5 mark and dilution liquid to the 101 mark for subsequent calculation of the initial number of thrombocytes. After this, a thrombocyto aggregating agent is added to the test tube and at the same time a stopwatch is started. After 1, 15 and 25 minutes, blood is taken again to count thrombocytes.

When blood is taken from a siliconized microtube at the 15th minute of the study, the metal rod is transferred to a non-siliconized microtube. After 5 and 10 minutes blood is drawn from this tube. The last taking of blood immediately follows the collection of blood from the siliconized microtube at the 25th minute to evaluate the results of thrombocyte aggregation and adhesion, the number of thrombocytes contained in the blood taken from the siliconized microtube before the administration of the thrombocyte aggregating agent is taken as the initial thrombocytes count.

ADF from firm (Renal) was used as an aggregating agent. The ADF solution was stored in a refrigerator at 4°C and prepared once a week.

The degree of thrombocytes adhesion was determined after 5 and 10 minutes of blood contact with the glass of a non- siliconized microtube. The difference between the initial number of thrombocytes taken as 100% and the number of thrombocytes after 5 and 10 minutes of rotation and contact of blood with the inner surface of the tube was expressed in a percentage.

The thrombocytogram was studied according to the method of Piksanov (1966). The platelet formula was derived by counting the number of “young”, “mature”, “old” and degenerative, vacuolated forms of thrombocytes, as well as forms of irritation.

The obtained results were processed by the method of variation statistics with the calculation of Student's criteria for the significance of differences.

CHAPTER III. INFLUENCE OF BARBERRY VULGARIS PREPARATIONS ON THE MEGAKARYOCYTIC-THROMBOCYTES' SYSTEM OF RATS

III.1. Comparative study of preparations of barberry vulgaris and yarrow on the number of thrombocytes in the peripheral blood of rats.

Before the administration of barberry root decoction the average thrombocytes' count was 306.0x109/l (100%) in the second group of animals. A significant increase in the number of thrombocytes was observed in 1 and 3 days after administration of the drug and constituted 620.0x109/l (203%) and 830.0x109/l (271%), respectively. Starting from the sixth day there was a decrease in the blood platelets' count up to to 550.0 x 109/l, what remained 80% higher than the initial level. After 10 days the decrease in the count of thrombocytes constituted 408.0x109/l, it was 33% higher than the initial value.

In the third group of animals the count of thrombocytes before the administration of sodium chloride solution averaged 306.0x109/l (100%).

Table 3

Influence of barberry preparations and yarrow infusion on

the number of thrombocytes in the peripheral blood in intact rats Drugs administered to groups of animals	Statistical data	thrombocytes' count per 10^9/l				
		Before the administration	Days of observation after drug administration			
			1	3	6	10
Group I: solution of berberine bisulfite (=10)	M± % P<	306,0+9,0 100	687,0+6,0 224,5 35,0 0,001	883,0+8,0 288,5 48,0 0,001	703,0+7,0 230 35,0 0,001	430,0+4,0 141 13,0 0,001

Group II: decoction of barberry root	M± % P<	306,0+9,0 100	620,0+6,0 203,0 29,0 0,001	830,0+8,0 271 44,0 0,001	550,0+5,0 180 24,0 0,001	408,0+4,0 133 10,0 0,001
Group III: 0.9% saline sodium chloride solution	M± % P<	306,0+9,0 100	315,0+10,0 103 0,64 0,1	298,0+4,0 97 0,81 0,1	300,0+11,0 98 0,40 0,1	315,0+9,0 103 0,70 0,1
Group IV yarrow infusion	M± % P<	394,0+9,0 100	422,0+16,5 107 1,47 0,1	442,0+3,0 112 3,0 0,05	490,0+17,6 124 4,8 0,01	399,0+11,0 101 0,45 0,1

Observations during the 1-st, 3-d, 6-th and 10-th days showed that the number of thrombocytes in the peripheral blood of rats ranged within physiological parameters.

In the fourth group of animals the administration of yarrow infusion resulted into a maximum increase in the number of thrombocytes after 6 days (490.0x 109/l, 124%), while the administration of barberry preparations significantly increased the number of blood platelets from the 3rd day of observation.

The results of the studies revealed a platelet-stimulating effect in preparations of barberry and yarrow. At the same time, it should be emphasized that barberry preparations had the most thrombocytes-stimulating effect, what cannot be noted in case of yarrow usage.

III.2. Effect of barberry preparations on the number of megakaryocytes in the bone marrow of rats

To establish the truth of the thrombocytes-stimulating effect of barberry preparations it was necessary to find out their influence on the number of bone

marrow megakaryocytes, since the presence of an inverse relationship between the number of blood platelets and the number of bone marrow megakaryocytes had been approved (38,63).

According to some authors (60,70,163), the total transit time for megakaryocyte maturation is 60 hours. One megakaryocyte can produce from 1400 to 1500 blood platelets.

Other researchers consider that the transit time for megakaryocytes is reduced by 1.3-1.5 times under various influences, so these changes proved to be nonspecific response to any influence (64,163).

Under normal conditions, the process of platelet formation involves mainly polychromatophilic megakaryocytes, granular.

Our research on the influence of barberry vulgaris preparations on the megakaryocyte system of rats showed (Table 4) that the number of megakaryocytes in 1 mm 3 of bone marrow punctate increases under the influence of berberine sulfate. Thus, if before the administration of the drug the number of megakaryocytes constituted 87.4 (100%), then, after the first day of drug administration their count increased to an average of 131.0 (150%), after 3 days - to 176.0 (201% $P<0.001$), and after 6 days of observation there was a decrease to 122.0 (140%); on the 10-th day the number of megakaryocytes decreased to the initial level.

If the number of megakaryocytes before the administration of barberry root decoction averaged 87.0 (100%), then one day after administration their number increased to an average of 124.0 (142%), after 3 days - 140.0 (161%) , and after 6 and 10 days the number of megakaryocytes begins to decrease gradually, reaching the initial level (114.0; 130% and 87.0; 99.5%, respectively, days of observation).

Administration of saline solution (control) did not result into significant changes in the number of megakaryocytes (see Table 4). The results of counting smears showed that before the administration of berberine bisulfate the number of functioning megakaryocytes constituted on average 33.0 (100%), and after the 1-st, 3-d and 6-th days after administration their number statistically significantly

increased, respectively, to 55.0 (166.6%), 58.0% (165 .8%), 51.0 (164.5%), and on the 10-th day their number reached the initial level and constituted 39.0 (118.0%).

The number of functioning megakaryocytes after administration of barberry root decoction after the 1-st, 3-d and 6-th days increased significantly from 33.0 (100%) to 49.5 (150%), 52.0 (160%), 50.5 (153%), respectively, on the days of the study, and after 10 days there was a tendency to decrease to the initial level.

Analysis of the partial megakaryocytogram showed (Tables 4,5,6) that the increase in the number of functioning megakaryocytes was mainly due to an elevation in the number of polychromatophilic forms of megakaryocytes, which proved to be the most active cells of the megakaryocyte series. The number of basophilic forms of megakaryocytes, that is, “young” forms of megakaryocytes, had slightly increased.

Thus, the results of our experimental studies demonstrated that the count of thrombocytes in the peripheral blood of rats as well as megakaryocytes in the bone marrow showed that barberry preparations, when administered once, have a manifested true blood platelet-stimulating effect, this effect persists for 10 days of observation.

Table 4

Change in the number of megakaryocytes before and after administration of barberry vulgaris preparation to rats

Drugs administered to groups of animals	Statistical data	Number of megakaryocytes					
		Before administration		Days of observation after drug administrati			
		Megakaryocytes	Functioning from them	Megakariocytes	Functioning from them	Megakariocytes	Functioning from them

Group I: Berberine bisulfate solution (n =30)	M±m % T P<	87,4+7,8 100	33,0+3,0 100	131,0 +9,0 150 3,66 0,01	55,0+4, 5 166,6 4,1 0,01	176,0+7,0 201,3 8,51 0,001	58,0 +5,0 175,8 4,28 0,01
Group II: decoction of barberry root (n =30)	M±m % T P<	87,4+7,8 100	33,0+3,0 100	124,0 +7,7 142 3,35 0,01	49,5+4, 0 150 3,1 0,05	140,5+7,8 161 4,8 0,001	52,0 +5,0 160 3,27 0,01
III группа 0,9% Раствор хлорида натрия (n =30)	M±m % t P<	87,4+7,8 100	33,0+3,0 100	83,2+ 7,5 95 0,38 0,1	35,0+3, 5 106 0,43 0,1	85,2+7,8 97,4 0,2 0,1	33,0 +5,0 100 0,1

Drugs administered to groups of animals	Statistical data	Number of megakaryocytes			
		Before administration		Before administration	
		Megakariocytes	Functioning from them	Megakariocytes	Functioning from them
Group I: Berberine bisulfate solution (n =30)	M±m % T P<	122,0+6, 0 140 3,51 0,01	51,0+4,0 154,5 2,68 0,05	87,0+6,0 100 0,406 0,05	39,0+3,0 118 1,42 0,05
Group II: decoction of barberry root	M±m % T	114,0+4, 2 130,4	50,5+5,0 153 3	87,0+6,0 99,5 0,4	39,0+4,0 118 1,2

(n =30)	P<	3 0,05	0,05	0,,1	0,1
Group III 0.9% Sodium chloride solution (n =30)	M±m % t P<	82,3+7,1 94 0,48 0,1	32,5+4,0 98,4 1 0,1	86,5+6,5 98 0,089 0,1	34,0+3,0 103 0,23 0,1

III.3. Identification of the possible mechanism of action of barberry preparations on thrombocytopoiesis

At present, there is no doubts that thrombocytopoiesis is regulated with the help of humoral substances - thrombocytopoietins according to the feedback principle (38.71).

To clarify the possible mechanism of action of barberry preparations on thrombocytopoiesis, a number of experiments were carried out to identify the endogenous factor - thrombocytopoietin, since an increase in the number of platelets is preceded by the appearance of this factor (24,55) what had been convincingly approved by many researchers.

We assessed the thrombocytopoietic activity of the blood serum of donor animals (rats) by the severity of the increase in the count of thrombocytes in the peripheral blood as well as megakaryocytes in the bone marrow of rats.

The experimental results presented in Table No. 8 demonstrated that before the administration of the serum, the count of thrombocytes constituted 304.0x10 9 / l (100%); on the 1-st, 3-d 6-th days after the administration of the serum the count of thrombocytes in recipient rats significantly increased up to 530 .0x109/l (174.3%), 576.0x109/l (222.3%) and 475.0x109/l (156.2%), respectively, on the days of observation. By the 10-th day of observation, the blood platelet count reached the initial level and constituted 320.0x109 /l (105.2%).

The number of megakaryocytes in recipient rats (Table 8) on the first day after the administration of serum increased up to 184 (210.5%), after 3 days - 151 (172.7%), after 6 days - 100 (114.4%) and by day 10 the average number of megakaryocytes was 89 (101.8%), what was practically the same as the initial level.

Table 5

MEGAKARYOCYTOGRAM OF RATS BEFORE – AND AFTER ADMINISTRATION OF BERBERINE BISULPHATE (n =30)

Megakariocytes' form	Before administration		After administration через сутки							
			1		3		6		10	
	Abs.	%	Abs.	%	Abs.	%	Асб.	%	Абс.	%
Number of megakaryocytes in 1mm3 of bone marrow punctate, from which:	87,4	100	131	150	176	201	122	140	87	100
Fuctioning megakariocytes	33	100	55	167	58	176	51	155	39	118
Megakarioblasts	1	1	2,3	1,67	4,5	3	2	2	1	1
Basophil megakariocytes	27,3	31	41,5	31,68	59,5	34	40	33	31	36
Oxyphilic megakaryocytes	3	3,4	2,9	2,21	4,5	2	1	0,8	1	1
Polychromatophilic megakaryocytes	45,1	51,6	61,5	46,95	81	46,9	65	53	43	49
Involuting megakaryocytes	3	3	7,5	5,73	7,5	4	4	3,2	4	5
Free nuclea	9	10	15,3	11,68	19	11	10	8	7	8

Table 6

MEGAKARYOCYTOGRAM BEFORE AND AFTER ADMINISTRATION OF BARBERRY ROOT DECOTION

Megakariocytes' form	Before administration		After administration in a day							
			1		3		6		10	
	Абс.	%	Abs.	%	Abs.	%	Асб.	%	Абс.	%
Count of megakaryocytes in 1mm3 of bone marrow, from which:	87,4	100	124,4	153,3	140,5	168,5	114	130,4	108	123,6
Megakariocytes	1	1	3	2,4	2	1	1	1,5	1	0,9
Functioning megakarioblasts	33	100	49,5	100	52	158	50,5	155	36	109
Basophilic megakaryocytes	27,3	31	33	27	43	31	31	27	32	30
oxyphilic megakaryocytes	3	3,4	2	2	2,5	2	1,5	1	1	0,9
polychromatophilic megakaryocytes	45,1	51,6	65	52	68	481	61	54	57	53
Involutive megakaryocytes	3	3	8	6,4	10	7	9	8	7	6,2
Free nuclea	9	10	13	10,2	15	11	10	9	10	9

Table 7

MEGAKARYOCYTOGRAM OF RATS BEFORE AND AFTER ADMINISTRATION OF 0.9% SODIUM CHLORIDE SOLUTION (n =30)

Megakariocytes' form	Before administration		After administration in a day							
			1		3		6		10	
	Абс.	%	Abs.	%	Abs.	%	Асб.	%	Абс.	%
Count of megakaryocytes in 1mm3 of bone marrow, from which:	87,4	100	87,4	100	83,2	95	85,2	97,4	86,5	98,9
Megakariocytes	33,0	100	33,0	100	35,0	106	32,5	98	34	103
Functioning megakarioblasts	1,0	1,1	1	1,14	1	1,2	1	1,17	1	1,15
Basophilic megakaryocytes	27,3	31	28,2	32,2	30	36,05	30,3	35,56	31,3	36,11
oxyphilic megakaryocytes	3,0	3,4	2	2,29	2	2,4	2	2,34	2	2,31
polychromatophilic megakaryocytes	45,1	51,6	46,2	52,86	40,2	48,3	39,8	46,71	40,2	46,47
Involutive megakaryocytes	3,0	3	3	3,43	2,0	2,4	3	3,52	3	3,46
Free nuclea	9,0	10	7	8	8	98,6	9,1	10,68	9	10,4

The data presented in Table 8, show that before the introduction of serum from donors who received a decoction of barberry root, the thrombocytes'count constituted

304.0x109/l. (100%); after the first day after its single administration, the number of blood platelets increased to 525.0x109/l (172.6%); after the 3-d day the increase in the number of thrombocytes in recipient rats reached 760.0x109/l (250%); after the 6-th day it was 650.0x109/l (213.8%, P<0.01) and on the 10-th day the blood platelets count decreased, but it never reached the initial level and constituted 350.0x109/l (115%).

The data obtained and presented in Table 8, demonstrate that before the introduction of serum from donors who received a decoction of barberry root, the thrombocytes' count constituted 304.0x109/l. (100%). After the first day after its single administration, the number of blood platelets increased up to 525.0x109/l (172.6%); after 3 days the increase in the number of thrombocytes in recipient rats reached 760.0x109/l (250%). On the 6-th day it was 650.0x109/l (213.8%, P<0.01) and on the 10-th day the blood platelets count decreased, but it never reached the initial level and constituted 350.0x109/l (115%).

In the same rats, the number of megakaryocytes constituted approximately 87.4 (100%). On the first day after the administration of serum, the number of megakaryocytes increased significantly and constituted to an average of 253.0 (289%); after the 3-d day the increase in the number of megakaryocytes reached an average of 179.0 (204.8%) (P < 0.01). After the 6-th and 10-th days a significant decrease was noted with values leveling off close to the initial ones (100.0 or 114.4% and 89.0 or 101.8%, respectively, on the 6-th and 10-th days of the study).

Table 8

THE INFLUENCE OF DONOR RATS' SERUM UNDERGONE BARBERRY VULGARIS PREPARATIONS ON THE THROMBOCYTES COUNT IN PERIPHERAL BLOOD AND MEGAKARYOCYTES IN THE BONE MARROW OF RECIPIENT

Serum introduction from donors who were given:	Statistic data	Before administration		Observation days after administration			
		T	M	The 1-st day		The 3-d day	
				T	M	T	M
Group 1: Berberine bisulfate (n=20)	M+m % T P<	304,0+9,0 100	87,4+8,0 100	530,0+5,0 174,3 22,6 0,001	184,0+8,0 210,5 4,9 0,001	6766,0+7,0 222,3 33,8 0,001	151,0+14,0 172,7 3,9 0,001
Group 2: Decoction of barberry root (n=20)	M+m % T P<	304,0+9,0 100	87,4+8,0 100	525,0+4,0 172,6 22,5 0,001	253,0+20,0 289 21,5 0,001	760,0+7,0 280 35,0 0,001	179,0+10 204,8 7,15 0,001
Group 3: 0.9% sodium chloride solution (n=20)	M+m % T P<	304,0+9,0 100	87,4+8,0 100	293,0+3,0 96,3 1,2 0,1	87,4+8,0 100 0 0,1	319,0+11,0 105 1,05 0,1	83,2+6,095 0,42 0,1

Continuation of table 8

Serum introduction from donors who were given:	Statistic data	Observation days after administration			
		The 6-th day		The 10-th day	
		T	M	T	M

Group 1: Berberine bisulfate (n=20)	M+m % T P<	475,0+ 5,0 156,2 17,0 0,001	100,0 +9,0 114,4 1,05 0,1	320,0+ 4,0 105,2 1,6 0,2	89,0+5,0 101,8 0,14 0,1
Group 2: Decoction of barberry root (n=20)	M+m % T P<	650,0+ 16,0 213,8 32,0 0,001	100,0 +9,0 114,4 1,05 0,1	350,0+ 5,0 115,0 4,5 0,01	89,0+8,0 101,8 0,14 0,1
Group 3: 0.9% sodium chloride solution (n=20)	M+m % T P<	296,0+ 2,0 97 0,86 0,1	85,2+ 5,0 97 0,23 0,1	298,0+ 5,0 98 0,58 0,1	86,5+5,0 99 0,95 0,1

In the control group of recipient rats, the administration of serum from donors who received physiological solution did not cause significant changes in the number of thrombocytes in the peripheral blood or megakaryocytes in the bone marrow at any time during the study.

These experiments showed a synchronicity in the increase in the number of thrombocytes and megakaryocytes after the administration of barberry preparations and the administration of serum from donors who received the same preparations. Thus, our results gave the possibility to assume that one of the possible mechanisms for stimulating thrombocytopoiesis is carried out through thrombotopoietins.

N.V. Traskunova and co-authors (1975) were the first to mention the thrombocytopoietic factor in patients suffering from thrombocytopenic purpura, remission was obtained due to the humoral factor that can stimulate thrombocytopoiesis.

Thrombocytopoietic factor was also found in the plasma of animals after blood loss. It was found that after the administration of serum from people who had suffered massive blood loss to experimental animals (rabbits), the number of thrombocytes in

the peripheral blood increased in the latter. Serum from healthy people did not cause such an effect (38.71).

Statistic data	Primary data	Observation days after serum introduction

Therefore, human serum after blood loss contains thrombocytopoietin which proved to be a blood platelet-stimulating factor. Essentially, this work was an example of a biological test for the detection of thrombocytopoietins using a test object (recipient) of rabbits. Biological method, which currently forms the basis of existing methods for determining thrombocytopoietic activity, differs in the nature of the test material administered (serum, plasma, plasma filtrate, bone marrow extract, duodenal juice) as well as in the type of recipient animals used (rats, mice, guinea pigs). In addition to plasma, thrombocatopoietic activity was found in duodenal juice and urine (38.74).

Thrombocytopoietic activity of the material is evaluated by the degree of increase in the number of thrombocytes in the peripheral blood of the recipient animal. Considering the above, to confirm the fact of blood platelet-stimulating effect of barberry preparations, we used a biological method, that is, serum from donor patients, receiving studied drugs were administered to recipient rats.

To obtain the serum, 10 ml of blood was taken from the patient’s vein into a sterile tube which was used during an hour. Control group of animals was injected with serum from practically healthy people, as well as a solution of 0.9% sodium chloride. Experimental group was injected with serum from patients who took barberry preparations. Donor serum and physiological solution were administered once, intraperitoneally at the rate of 1 gm/100 g body weight of rats.

		Before preparation administration			After preparation administration			
		1	3	6	1	3	6	10
		Berberine bisulfate						
M+m	314,0+20,0	387,0+3,0	381,0+7,0	335,0+3,0	727,0+31,0	730,0+19,0	689,0+8,0	471,0+8,0
%	100	123	121	106	217	218	206	141
T		3,65	3,10	1,05	13,0	21,0	39,0	15,0
P<		0,01	0,01	0,1	0,001	0,001	0,01	0,001
N = 10								
		Decoction of barberry root						
M+m	314,0+20,0	380,0+4,0	390,0+6,0	342,0+4,0	745,0+28,0	750,0+23,0	678,0+8,0	460,0+7,0
%	100	121	124	108,9	230	231	198	134,5
T		3,3	3,6	1,3	16,0	19,0	37,7	14,7
P<		0,01	0,01	0,1	0,001	0,001	0,001	0,001
N = 10								

Table 9

INFLUENCE OF SERUM OF PATIENTS WITH THROMBOCYTOPENIA

Continuation of table 9

Statistic data	Primary data	Observation days after serum introduction						
		Before preparation administration			After preparation administration			
		1	3	6	1	3	6	10
		Berberine bisulfate						
M+m	338,0+11,0	352,0+9,0	360,0+10,0	344,0+8,0	380,0+9,0	368,0+9,0	368,0+11,0	356,0+6,0
%	100	104	107	101,7	110	107	106	103
T		1,42	1,48	0,44	1,3	1,76	1,76	1,2
P<		0,1	0,1	0,1	0,1	0,1	0,1	0,1

N = 10								
M+m	399,0+70,0	Decoction of barberry root						
		427,0+9,0	407,0+7,	388,0+8,	420,0+8,	400,0+	407,0+	390,0
%	1000		0	0	0	7,0	8,0	+8,0
T		107	102	97	108	103	105	100,5
P<		2,5	0,8	1,03	2,6	1,13	1,68	0,176
N = 10		0,05	0,1	0,1	0,05	0,1	0,1	0,1

Table 9 presents data characterizing changes in the thrombocytes' count in control animals, as well as animals after intraperitoneal administration of serum from donor patients who received berberine bisulfate and a decoction of barberry root. As can be seen from the table above, the number of thrombocytes in the peripheral blood of rats increased significantly throughout the day of observation.

For example, in the experimental group of animals, the number of thrombocytes before the administration of blood serum from a patient who had not yet taken berberine bisulfate constituted 314.0x109/l (100%); on the first day after administration their number increased to an average of 387.0x109/l (123%), after the 3-d day their number practically remained at the same level noted on the 1st day after the administration of the serum, that is, 381.0x109 /l (12I%), and on the 6th day of observation it slightly decreased (335.0x109 /l (106.6%) reaching the initial value.

The same group of animals was again injected with serum from the patient, who received berberine bisulfate during 5 days. One day after the repeated administration of serum, the number of thrombocytes in these animals increased and constituted 27.0x109/l (217%); after 3 days it continued to remain at the same level, that is, 730.0x109/l (218%), and after 6 days, a slight decrease was noted and constituted 689.0x109/l (206%); after 10 days the number of blood platelets

continued decreasing, but it was 41% higher than the initial level, i.e. in absolute terms, their number constituted 471.0x109/l.

The second group of animals was similarly injected with serum from a patient who had taken a decoction of barberry root. Injecting rats with the blood serum of a patient with thrombocytopenia, who had not yet taken a decoction of barberry root, significantly increased the blood platelets' content. Thus, if the thrombocytes' count before the administration of serum was 314.0x109/l (100%), then 1, 3, 6 days after the administration of serum the number of blood platelets constituted 380.0x109 (121%), 390.0x109/l (124, 5), 342.0x10 9/l (108.9%) according to the days of observation.

After a decrease in the number of platelets in the peripheral blood, from day 6, the same group of animals was again injected with serum from the same patient who received a decoction of common root for 5 days. After 1 and 3 days after the administration of such serum, the number of blood platelets in animals increased significantly and reached 745.0x109/l (230%); 750.0x109/l (231%), respectively; after 6 days it slightly decreased, amounting to 678.0x109/l (198%) and by the 10th day of observation - 460.0x109/l (134.5%).

In the third group of rats before the administration of saline solution thrombocutes' count averaged 338.0x109/l (100%); on the 1-st, 3-d and 6-th days after its administration blood platelets' count was 352.0x109/l (104%), 360.0x109/ l (107%), 344.0x109/l (101.7%), respectively. Starting from the last day of observation physiological solution was reintroduced. After the 1-st, 3-d, 6-th and 10-th days after repeated administration of platelets, the average data constituted 380.0x109/l (110%), 368.0x109/l (107%), 365.0x109/l (106%), 306.0x109/ l (103%) according to the days of observation, although a slight increase in the number of thrombocytes in the peripheral blood was noted in the control group; but this increase turned out to be a statistically insignificant value compared to the primary data.

As for the blood platelets reaction after the administration of blood serum from healthy people, a slight increase in the number of thrombocytes in the peripheral blood can be noted only on the 3-d day after both the primary and secondary

administration of the serum to recipient animals. Apparently, the noted increase is the result of the body's reaction to the introduction of a foreign protein.

Thus, we assume that the stimulation of thrombocytopoiesis by barberry preparations occurs due to thrombocytopoietins, which, according to the classification of A. L. Markosyan (1965), should be classified as long-acting thrombocytopoietins since they stimulate thrombocytopoietic function of the bone marrow, as our special studies have recently demonstrated(see above). Consequently, the results of our research suggest that barberry preparations proved to be natural stimulators of thrombocytopoiesis which gives us possibility to recommend them for the treatment of patients with thrombocytopenia of various origins.

CHAPTER IV

INFLUENCE OF BARBERIS VULGARIS PREPARATIONS ON THE NUMBER OF THROMBOCYTES IN PERIPHERAL BLOOD IN PATIENTS WITH IDIOPATHIC THROMBOCYTOPENIC PURPURA AND THROMBOCYTOPENIA OF DIFFERENT ORIGIN

IV.1. Effect of barberry vulgaris preparations on the number of thrombocytes in peripheral blood in patients with idiopathic thrombocytopenic purpura

According to the used therapy and the effectiveness of treatment all patients with ITP were divided into the following groups:

Group 1 patients received only berberine bisulfate,

Group 2 patients received only a decoction of barberry vulgaris root,

Group 3 of patients received preparations of barberry vulgaris and prednisolone, intravenous - E-ACC, thrombocyte and erythrocyte mass,

Group 4 of patients - control, received only traditional therapy.

Due to the fact that in ITP the transfusion of thrombocyte concentrate should be done very carefully, since this disease is often of autoimmune origin (89,97,156), we

performed thrombocyte transfusion only in 24 cases. This was very important, since the hemorrhagic syndrome, despite intensive therapy with hormonal and hemostatic agents, as well as taking barberry vulgaris preparations, did not stop. After transfusion of thrombocyte concentrate, there was a decrease in bleeding and a gradual increase in the number of thrombocytes in the peripheral blood.

The indication for intravenous infusion of single-group red blood cells was the presence of severe posthemorrhagic anemic syndrome in patients.

From the data presented in Tables 10 and 11 it is clearly shown that barberry vulgaris preparations significantly (P.<0.05) increase the number of thrombocytes in the peripheral blood during all days of observation.

Thus, in the first group of patients, before taking the drug berberine bisulfate, the thrombocytes count was 101.0x109/l (100%), 5 days after taking it, the thrombocytes count increased to 144.0x109/l (143%), after 10 days - 170.0x109/l (168%), after 15 days this increase averaged 189.0x109/l (187%).

In patients of the second group, before giving the drug in the form of a decoction of barberry vulgaris root the number of thrombocytes was 110.0x109/l (100%), on the 5th day after taking the drug their number reached 140.0x109/l (127%), after 10 and 15 days the thrombocytes count was 167.0x109/l (152%) and 184.0x109/l (167%), respectively ($P < 0.05$).

In patients of the third group before starting the treatment thrombocytes count was 81.0x109/l (100%), 5, 10 and 15 days after treatment the number of thrombocytes increased up to 114.0x109/l (141%), 135.0x109/l (167%) and 144.0x109/l (178%), respectively. In patients of the fourth group (control) before treatment the thrombocytes count averaged 105.0x109/l (106%), after 5, 10 and 15 days the platelet count averaged up to 104.0x109/l (99%), 138.0x109/l (131%) and 113.0x109/l (107.6%), respectively during the days of study.

There is a short extract from the medical history of two patients with ITP who were taking drugs of barberry vulgaris. Patient Kh.A., born in 1974, is sick from 8-year-old, his disease began with nosebleedings. He was repeatedly treated for chronic ITP in the hematology department of Children's Hospital No. 1 in Andijan. He took

glucocorticoids and hemostatic drugs. He was admitted to the clinic on September 10, 1991 with medical history 17324/1139. On admission he complained of spontaneous nosebleedings, petichial rash formation on the skin, and periodic gum bleedings. While clinical examination of internal organs no changes were found. General analyses of blood: NV - 120 g/l, erythrocytes - 4.6; color index - 0.9; leukocytes - 5.8; p/i - I, s/i - 68, eosinophils - 2, lymphocytes - 4, monocytes - 4; erythrocyte sedimentation rate - 2 mm/hour. Urinalysis was unchanged. Thrombocytes on admission I08.9xI09/l. Pinch and tourniquet symptoms were positive.

CHANGES IN THE NUMBER OF THROMBOCYTES IN PERIPHERAL BLOOD OF PATIENTS WITH ITP UNDER THE INFLUENCE OF BERBERINE BISULPHATE (A) AND BARBERRY VULGARIS ROOT DECOCTION (B)

Table 10

Statistical indicators	The number of thrombocytes $x10^9$ /л			
	Before taking the drug	Days of obsrevation		
		5	10	15
A				
M+m	101,0+0,9	144,0+13,0	170,0+9,0	189,0+12,0
%	100	143	168	187
t		3,0	3,0	6,0
P<		0,01	0,01	0,001
N = 27				
Б				
M+m	110,0+10	140,0+11,0	167,0+9,0	184,0+9,0
% T	100	127	152	167
P<		2,0	4,0	6,0
N=24		0,05	0,001	0,001

CHANGES IN THE NUMBER OF THROMBOCYTES IN PERIPHERAL BLOOD OF PATIENTS WITH ITP UNDER THE INFLUENCE OF COMPLEX TREATMENT (A) AND TRADITIONAL TREATMENT METHODS (B)

Table 11

Statistical indicators	The number of thrombocytes x10^9 /л			
	Before taking the drug	Days of obsrevation		
		5	10	15
A				
M+m	81,0+12,0	114,0+13,0	135,0+17,0	144,0+15,0
%	100	141	167	178
t		1,41	2,5	3,3
P<N = 14		0,05	0,05	0,01
Б				
M+m	105,0+8,0	104,0+11,0	138,0+13,0	113,0+6,0
%	100	99	131	107,6
T		0,07	2,17	0,8
P<N=10		0,1	0,05	0,1

Bleeding time according to Duques, capillary blood clotting time according to Sukharev: beginning - 180", end - 245". Thrombocytes adhesion before taking the drug berberine bisulfate; h5 -18%, h10-61%. Thrombocytes aggregation before taking berberine bisulfate induced by the addition of ADP: hH -46%, hM-73%, hd - I00%.

Clinical diagnosis:

Idiopathic thrombocytopenric purpura. Chronic form. Light flow.

After treatment with berberine bisulfate (5 mg, 3 times a day for the period of 15 days), the patient’s condition improved, the nosebleedings stopped and the gums bleeding stopped. Skin petichial rashes have disappeared. Symptoms of tourniquet and pinch are negative. The thrombocytes count after 5 days taking berberine

bisulfate increased to 124.0x10 9/l (114.5%), after 10 days - 132.0x10 9/l (122.2%), after 15 days an increase in the number of thrombocytes in peripheral blood amounted to 170.0x10 9/l (157.4%).

According to Sukharev, the clotting time of capillary blood accelerated after taking the drug 5 days: beginning - 130", end - 155", after 10 and 15 days, the acceleration of capillary blood clotting reached: beginning - 120", end - 150", and beginning - 150", end - 210% according to the days of observation.

The functional state of thrombocytes changed according to following data. Thrombocytes adhesion after taking berberine bisulfate 5 days was h5-61%, h10-74%, it practically did not change after 10 days in comparison to the 5th day of observation: h5-59%, and at the 10th minute, on the contrary, it increased and reached 82%; after 15 days, changes in adhesive function showed the following data: h5-50%, h10 -56%.

The dynamics of changes in thrombocytes aggregation function showed the following data: after 5 days hH-49%, hM-78%, hd-31%; after 10 days hH -52%, hM -11%, hd-29% after 15 days h H-43%, hM-11%, hd -42%.

2. Patient O.V., 57 years old. She received treatment at clinic 1 MSO-8 in Obninsk city, registration journal number 43 of the clinical diagnostic laboratory of the Russian Medical Research Center of the Russian Academy of Medical Sciences. She has been ill for over 15 years, has repeatedly taken hormone therapy, vasoconstrictor and hemostatic drugs,

At present time the patient suffers from nosebleedings, the appearance of petechial rashes on the skin, and bleeding from the uterus. After a thorough examination, the patient was diagnosed ITP. Chronic course.

Before administration of berberine bisulfate the thrombocytes count was 30.0 x 109/L (100%), after 5 days the thrombocytes count increased to 56.0 x 109/L (186.1%), after 10 days the thrombocytes level increased to 98.0x109/l (326.6%) the thrombocytes number reached its maximum after 15 days and was equal to 152.0x109/l (506.6%).

Before prescribing berberine bisulfate thrombocytes adhesive-aggregation function was: h5 -42%, h10 -58/%, aggregation - hH-58%, hм-58%, hд – 0%, after 5 days thrombocytes adhesive function changed as follows: h5–51%, h10–82%; after 10 days h5-80%, h10–86% ; after 15 days h5- 69%, h10- 47%.

Aggregation and disaggregation activity of thrombocytes during treatment increased as follows: after 5 days h -83 5, h -90%t h -Q%; after 10 we give h n m d; n

In both cases, bleeding of various localizations stopped, skin petichial rashes disappeared. The patients' general condition improved. A comparative analysis of treatment of patients with ITP with barberry preparations for 15 days showed that the greatest positive effect was observed with berberine bisulfate rather than with a decoction of barberry vulgaris root. After taking barberry vulgaris preparations, as shown in Figure 2, the number of young and mature forms of thrombocytes increases on the 5th and 10th days of observation.

Summarizing the results of the observation, we can draw the following conclusion: in patients with ITP, berberine bisulfate and decoction of barberry vulgaris root increase the number of thrombocytes in the peripheral blood ($P < 0.05$), shorten the time of primary bleeding, accelerate the clotting time of capillary blood and results in an increase of functional activity of thrombocytes.

On the basis of above mentioned facts we recommend clinicians to administer barberry vulgaris preparations to patients with ITP for therapeutic purposes and to prevent recurrence of the disease.

IV.2. The effect of barberry vulgaris preparations on the number of thrombocytes in patients with anemia of various etiologies with symptomatic thrombocytopenia

62 patients were included in this group; 33 patients - with hereditary hemolytic anemia, 19 patients - with polydeficiency anemia, 10 patients (control group) - patients with polydeficiency anemia, who were treated by traditional method of treatment without barberry vulgaris preparations.

Patients with hereditary hemolytic anemia were divided into 2 groups: the first group took the drug berberine bisulfate 5 mg 3 times a day, 30 minutes before meals during a period of 15 days; the second group received the drug in the form of a decoction of barberry vulgaris root, 1 tablespoonful 3 times a day as well as for 15 days.

In the first group of patients with hereditary hemolytic anemia with symptomatic thrombocytopenia, before taking berberine bisulfate, the number of thrombocytes in the peripheral blood averaged 114.0x109/l (100%), after 5 days of taking the drug their number increased to 153.0x109/l (134 %), after 10 and 15 days the number of blood platelets averaged 171.0x109/l (148%) and 178.0x109/l (156%), respectively.

These highly statistically reliable data are shown in Table 12 and indicate that the stimulating effect on thrombocytopoiesis is clearly expressed in patients who took the drug in the form of berberine bisulfate.

In the second group of patients, the thrombocytes count before taking the drug was 121.0xI09/l (100%), after taking 5 days the number of thrombocytes increased to 163.0x109/l (135%), after taking 10 days this increase averaged 186.0x109/l (154%), after 15 days it remained almost at the same level - 75.0x109/l (145%). These data are shown in Table 12 and they also indicate the stimulating effect of the drug taken by patients in the form of a decoction.

We decided to use data from the medical history of patient I.Kh., born in 1967, as an example to such situation. Case history number 1658/73. The patient is sick since childhood. She was registered for hereditary hemolytic anemia with symptomatic thrombocytopenia (B-thalassemia minor). On admission to the clinical hospital the patient complained on periodic nosebleedings, heavy uterine bleeding during menstruation-metrorrhagia, and the appearance of petichial rashes on the skin.

During objective medical examination there were petichial rashes on the skin, mainly on the forearm and legs. Examination of the internal organs: lungs and heart revealed no changes. The liver was enlarged to 4 cm, the spleen was enlarged to 10 cm. The results of USI dated January 18, 1991 - the spleen was enlarged, extends from the hypochondrium by 8-10 cm, the liver was +4 cm. Blood analysis dated

January 23, 1991. : HB - 12.5 g/l, er - 2.72x1012/l, color. -0.4; leukemia – 1.6x109/l, ESR – 8 mm/hour. In a blood smear, morphological examination revealed target-shaped red blood cells.

CHANGES IN THE NUMBER OF THROMBOCYTES IN PERIPHERAL BLOOD OF PATIENTS WITH HEREDITARY HEMOLYTIC ANEMIA WITH SYMPTOMATIC THROMBOCYTOPENIA DUE TO THE INFLUENCE OF BERBERINE BISULPHATE (A) AND BARBERRY VULGARIS ROOT DECOCTION (B)

Table 12

Statistical indicators	The number of thrombocytes x10^9 /л			
	Before taking the drug	Days of obsrevation		
		5	10	15
A				
M+m	140,0+4,0	153,0+5,0	171,0+7,0	178,0+6,0
%	100	134	149	156
t		6,0	6,0	8,0
P<		0,001	0,001	0,001
N = 20				
Б				
M+m	121,0+6,0	163,0+9,0	186,0+11,0	175,0+6,0
%	100	135	154	145
T		3,8	5,2	6,4
P<		0,01	0,001	0,001
N=13				

The number of platelets during the first course of treatment before the administration of the drug berberine bisulfate was 120.0x109/l, after 5 days of taking the drug their number increased to 160.0x109/l (133.3%), after 10 days it remained at the same level, after 15 days it reached 180.0x109/l (I50%).

After 1 month, the platelet count decreased to 100.0x109/l (83.4%), but no nosebleedings or extravasations on the skin were noted; during menstruation bleeding decreased. A splenectomy operation was planned due to the decrease in the number of thrombocytes and according to the previous regimen a second course of treatment with the drug berberine bisulfate was carried out. After 5 days taking the drug, the thrombocytes count reached 120.0x10 9/l (120%), after 10, 15 days the increase in thrombocytes count was 140.0x10 9/l (140%) and 180.0x10 9/l (180%), respectively.

After a second course of treatment splenectomy operation was performed. There was no bleeding during the operation or in the postoperative period; the thrombocytes count after the operation was at the level of 170.0 x 10 9/l. 10, 20 and 30 days after surgery the thrombocytes count was 190.0x10 9/l, 190.0x10 9/l and 178.0x10 9/l, respectively.

The above mentioned facts allowed us to come to the conclusion that barberry vulgaris preparations should be prescribed for the patients with hereditary hemolytic anemia with symptomatic thrombocytopenia and even for the patients who are getting ready to splenectomy operation.

As it is known pathologies of the gastrointestinal tract and liver, in which there is often deficiency of vitamin B12 and folic acid, iron, as well as essential proteins, which ultimately leads to the so-called polydeficiency anemia in are often found our region.

According to B.H. Khamzaliev (1983) opinion polydeficiency anemia, which occurs as a result of a simultaneous deficiency of vitamin C, B12, folic acid, iron, protein and some amino acids, thrombocytopenia does not occur immediately. Sufficiently high compensatory and adaptive capabilities of the body can hide the clinical manifestation of this pathology for a long time (77).

Iron deficiency anemia is a widespread disease, especially among women 80-95% (80). In this pathology the content of iron in the blood serum, bone marrow and depot organs (liver, spleen) decreases. As a result, the formation of hemoglobin and erythrocytes is disrupted. Long-term iron deficiency in the body results in

hyporegeneration of the bone marrow, hematopoietic organs, and hematopoietic tissue. This is the reason for the tendency to thrombocytopenia (77, 81).

Taking into consideration the above mentioned facts, we began examining and treating patients with polydeficiency anemia with symptomatic thrombocytopenia. Patients in this group took berberine bisulfate, as well as B vitamins, folic acid, and iron supplements. The control group of patients received only etiopathogenetic therapy.

The data obtained are shown in Figure 3 from which it can be seen that in these patients the number of thrombocytes in the peripheral blood increased. Thus, before taking the drug, the number of thrombocytes varied on average 128.0x10 9/l (100%), after 5, 10 and 15 days taking it the number of thrombocytes on average increased to 178.0x10 9/l (139%), 193.0x10 9/ l (150%), 204.0x10 9/l (195%) according to the days of the study.

In the control group of patients, before etiopathogenetic therapy the thrombocytes count averaged 120.0x10 9/l (100%), after 5, 10 and 15 days the increase in thrombocytes number, respectively, averaged 150.0x10 9/l (125%), 170.0x10 9/l (141.6%) and 170.0x10 9/l (141.6%).

Thus, performed research works allowed us to make conclusion that along with etiopathogenetic therapy barberry vulgaris preparations should be prescribed to correct symptomatic thrombocytopenia in patients with this pathology.

IV.3. The effect of barberry vulgaris preparations on the number of thrombocytes in peripheral blood in patients with hematopoietic depression

This group included patients with hypoplastic anemia and patients with leukemia. Hypoplastic anemia is a heterogeneous group of blood system diseases the basis of which is a decrease in projection bone marrow cells, usually three cellular elements (erythrocytes, leukocytes and thrombocytes lines)* One of the reasons for the development of cytopenia in hypoplastic anemia is functional defective stem cells and ineffective granulocytopoiesis (142).

In case of hypoplastic anemia there is a metabolic disorder in the cell, a change in the functional state of its membrane and the influence of an external factor - increased hemolytic activity of the serum and its toxicity. The result of such condition is the occurrence of a hemolytic component, both intracerebral and peripheral in 90% of cases, and in 10% of cases - a type of paroxysmal night hemoglobinuria.

The pathogenesis of hemorrhages, which sometimes take the main place in the clinical picture of the disease, is caused by deep thrombocytopenia and associated changes in the coagulation system, namely thrombocytes formation, thrombocytes adhesion and aggregation, and blood clot retraction. In the genesis of bleeding, a certain role is given to a disturbance of the metabolism of the vascular wall, leading to increased permeability due to a impairment of the angiotraffic function of thrombocytes (26, 83).

Bleeding is often the direct cause of patients' death (81) in hypoaplastic anemia.

The severity of hemorrhagic manifestations is determined by both the degree of thrombocytopenia and the qualitative inferiority of thrombocytes with a disturbance of their hemostatic function (24).

Hypoplastic anemia is characterized not only by quantitative, but also qualitative changes in cellular elements. Blood platelets are essential in maintaining normal vascular resistance. At the same time thrombocytes penetrating into endothelial cells release biologically active substances into them including factors III and V, which normalizes the functions of the capillary wall (24,60).

In hypopaplastic anemia, a vicious circle occurs, i.e. the number of thrombocytes decreases, the walls of blood vessels change, the blood coagulation quality is impaired, and therefore, patients with hypoplastic anemia often experience profuse bleeding, often with a fatal outcome.

Considering this circumstance, we decided to study the effect of barberry vulgaris preparations in patients with hypoplastic anemia.

One group of patients (7) received berberine bisulfate tablets, the other group (6) received a decoction of barberry vulgaris root.

The data obtained during the study in a summarized form are presented in

CHANGES IN THE NUMBER OF THROMBOCYTES IN PERIPHERAL BLOOD OF PATIENTS WITH HYPOPLASTIC ANEMIA UNDER THE INFLUENCE OF BERBERINE BISULPHATE (A) AND BARBERRY VULGARIS ROOT DECOCTION (B)

Table 13

Statistical indicators	The number of thrombocytes x10^9 /л			
	Before taking the drug	Days of obsrevation		
		5	10	15
A				
M+m	58,0+8,0	127,0+16,0	150,0+13,0	133,0+11,0
%	100	165	195	173
t		2,0	3,0	2,0
P<		0,1	0,05	0,05
N = 7				
Б				
M+m	58,0+8,0	82,0+12,6	146,0+14,7	152,0+4,2
%	100	193	251,7	262
T		2,0	5,0	10,0
P<		0,1	0,01	0,001
N=6				

It is seen from the table that barberis vulgaris preparations have a stimulating effect on the process of thrombocytes formation, especially after 10 days of taking the drug in patients with hypoplastic anemia.

From our point of view, patients who received barberis vulgaris preparations two times are of particular interest, as an example, we presented below data of patient M.N. born in 1975. Case history 30564/1547. Diagnosis: Hypoplastic anemia. Subacute form. Moderate severity.

The first course of patient's treatment consisted from taking berberine bisulfate 5 mg 3 times a day without hormones. Before administering the drug, the thrombocytes count was 40x109/l, bleeding time according to Duque was 20 minutes; after 5 days of receiving the drug the thrombocytes count reached 120 x 109/l, bleeding time was shortened to 5 minutes 30 seconds; after 10 days, the thrombocytes count was 130x109/l, bleeding time was 4 minutes 30 seconds. On the 15th day, the thrombocytes count reached 150x109/l.

After 12 days of the first course of treatment, the thrombocytes count decreased to 100x109/l, while the thrombocytes count was 2.5 times higher than the initial data. Starting from that day berberine bisulfate was re-prescribed according to the same regimen. At the same time on the 5th, 10th, 15th days of taking the drug, a significant, statistically significant increase in the number of thrombocytes was noted: 140x109/l, 180x109/l and 160xI09/l, respectively to the days of observation.

Thus, obtained data indicated that patients in this group should be prescribed preparations of barberis vulgaris.

A natural decrease in the number of thrombocytes in the blood during acute leukemia allowed most authors to believe that the basis of hemorrhagic phenomena in this disease most often lies on damage of the megakaryocyte- thrombocytes apparatus (57, 65, 182). This was also confirmed by the nature of bleeding - the predominance of petechial-spotted intradermal hemorrhages, nasal, uterine bleeding and bleeding from the gums in acute leukemia.

The idea has been repeatedly expressed that in acute leukemia there is also a qualitative inferiority of the blood thrombocytes, which play a significant role in the development of bleeding.

A deficiency of the third lamellar factor and impaired formation of thrombokinase of lamellar genesis are often detected (15, 18), and a decrease in the antiheparin activity of platelets has been noted in this disease. At the same time, significant but variable morphological and cytochemical changes in thrombocytes have been detected as well (76).

The maximum changes in the functional activity of thrombocytes were detected in patients with acute leukemia according to the works of other authors (82). The combination of these changes subsequently leads to the most dangerous complication of leukemia – severe bleeding due which it is very difficult to save patients.

Patients with leukemia under our supervision were prescribed berberine bisulfate simultaneously with cytostatic drugs in courses of VAMP (vincristine, amethopterin, 6-mercaptopurine, prednisolone) and CVAMP (cyclophosphamide, vincristine, amethopterin, 6-mercaptopurine, prednisolone) therapy.

The results of observations showed a significant increase in the number of thrombocytes in blood (Figure 4). It should be noted that in all patients the observed bleeding of various locations had stopped after taking the drug.

Patients of the control group received polychemotherapy and for the purpose of hemostatics, thrombomass, E-ACC, erythrocyte mass, etc. were infused intravenously; berberine bisulfate was not prescribed to these patients. Before treatment, the number of thrombocytes in blood averaged 116x109/l (100%), 5, 10, 15 days after treatment, the number of thrombocytes changed as follows: 97x109/l (83.6%), 81.0x109/l (69.8%), 109.0x109/l (94%) according to the days of observation.

The results of observations of individual patients with acute and chronic leukemia who received cytostatic and our proposed drugs were given as an example.

Patient H.0. 18 years. Case history No. 71/3. Diagnosis: Acute leukemia, undifferentiated variant. She took only berberane bisulfate for 5 days. The thrombocytes count from the initial level of 120x10 9/l increased to 220x10 9/l. Then the patient simultaneously received berberine bisulfate and VAMP therapy for 10 days. Although the thrombocytes count decreased to 190x10 9/l, it was significantly higher than the initial value (before starting the drug berberine bisulfate). On the 15th day of treatment (combined), although the thrombocytes count decreased again, it was 40% higher than the initial level.

Patient K.Sh. 42 years. Case history 13002/843. Diagnosis: Chronic myeloid leukemia. Expanded stage. Before taking the drug thrombocytes count was 140x10

9/l, 5 days after taking the drug their number was 150x10 9/l, after 10, 15 days after taking the drug the increase in thrombocytes count reached 190x10 9/l and 170x10 9/l, respectively, on the days of observation.

The presented data showed that berberine bisulfate had a stimulating effect on thrombocytopoiesis even while taking cytostatic drugs in patients with acute and chronic leukemia.

IV.4. Effect of berberine bisulfate on the number of thrombocytes in peripheral blood in patients with malignant lymphomas

Patients of this group along with chemoradiotherapy simultaneously took berberine bisulfate. This combination of therapy was performed in the hematology department of the Medical Research Institute of the Russian Academy of Medical Sciences (Obninsk) for the purpose of possible correction of thrombocytopenia that develops in patients with malignant lymphomas during cytostatic drug and (or) radiation therapy.

It is obviously that in patients who received berberine bisulfate the count of thrombocytes before taking the drug was 57.0x10 9/l (100%), 5, 10 and 15 days after taking the drug, the thrombocytes count was 3.0x10 9/l, (213%), P< 00.5; 119.0x10 9/l (206.5%) and 152.0x10 9/l (263.8%), P <0.05, respectively to the days of observation.

In the control group of patients, before treatment, the thrombocytes count was 61.0x10 9/l; 5, 10, 15 days after treatment, the thrombocytes count changed as follows: 62.0x10 9/l (101.6%), 71.0x10 9/l (116%), 78.0x10 9/l (128%) according to the days of observation.

As an example the medical history of patient A.N. is given. Born in 1937. She was treated in the hematology department of the MRRC RAMS in Obninsk. Diagnosis: Lymphogranulomatosis III" B" stage. She took the drug simultaneously with radiation and chemotherapy. Before taking the drug, the thrombocytes count was 64x10 9/l; after 5, 10 and 15 days, the thrombocytes count increased to 80x10 9/l

(125%), 76x10 9/l (118.8%) and I34xI0 9/l (209%) according to the days of observation.

According to the obtained results we came to the conclusion that the drug berberine bisulfate results in an increase in the number of thrombocytes during polychemotherapy, as well as during radiation therapy. Therefore, hematologists should prescribe berberine bisulfate to patients with malignant lymphomas during chemotherapy and radiation therapy in order to prevent a formidable complication of cytostatic therapy – thrombocytopenia.

IV.5. The effect of barberry preparations on the number of thrombocytes in peripheral blood of patients with liver pathology.

We examined 15 patients with liver disease. One group of patients (10) received the drug in the form of berberine bisulfate tablets 5 mg 3 times a day during the period of 15 days. Another group of patients (5) took the drug in an outpatient department in the form of a decoction of barberis vulgaris root, 1 tablespoon 3 times a day, during the period of 15 days.

In the first group of patients, before taking berberine bisulfate, the thrombocytes count was 109.0x109/l (100%), 5 days after taking the drug it increased to 149.0x109/l (137%), after 10 days the increase in thrombocytes count averaged 180.0x109/l (165%), after 15 days the thrombocytes count reached 196.0x109/l (150%) (Table 14).

Along with the positive effect of berberine bisulfate on thrombocytopoiesis, this group of patients showed an improvement in their general condition, disappearance of hemorrhagic syndromes, improved appetite, and increased patient activity.

Patients with liver cirrhosis (5), in addition to treatment in a hospital, were treated in an outpatient department with a decoction of barberry vulgaris root to prevent bleeding.

In this group of patients, before taking the root decoction of barberry vulgaris the thrombocytes count averaged 106.0x109/l (100%), 5 days after taking the drug the number of thrombocytes increased to an average of 146.0x109/l (I36%), after 10, 15 days the increase in the number of thrombocytes reached 180.0 x109/l (170%) and 203.0x109/l (192%) (Table 14).

CHANGES IN THE NUMBER OF THROMBOCYTES IN PERIPHERAL BLOOD OF PATIENTS WITH LIVER PATHOLOGY UNDER THE INFLUENCE OF BERBERINE BISULPHATE (A) AND BARBERIS VULGARIS ROOT DECOCTION (B)

Table 14

Statistical indicators	The number of thrombocytes $x10^9$ /л			
	Before taking the drug	Days of obsrevation		
		5	10	15
A				
M+m	109,0+7,0	149,0+13,0	180,0+15,0	196,0+1
%	100	137	165	7,0
t		3,3	4,3	180
P<		0,01	0,01	5,0
N = 10				0,001
Б				
M+m	106,0+11,0	146,0+16,0	180,0+22,0	203,0+2
%	100	135	170	2,0
T		2,1	3,0	192
P<		0,05	0,05	3,9
N=5				0,05

Along with a significant increase in the number of blood thrombocytes in patients, hemorrhagic symptoms disappeared, which is very important, from our point of view, since it allows on the one hand to treat such patients in an outpatient

department, and on the other hand it significantly reduces the percentage of occupied bed days in hospital for this category of patients.

As an example of patients with liver cirrhosis with thrombocytopenic symptoms who received several courses of treatment with barberry vulgaris preparations, we present a brief extract from the medical history of one patient.

Patient O.M. Born in 1973. Case history 20-07/127. Diagnosis: Splenomegalic cirrhosis of the liver. The first and second courses of treatment consisted of taking berberine bisulfate 5 mg 3 times a day for the period of 15 days; the third, fourth, fifth and sixth courses of treatment consisted of taking a decoction of barberry vulgaris root 1 tablespoon 3 times a day (the breaks between courses of treatment on an outpatient basis were 10 days). From Table 15 it can be seen that the clearly stimulating effect of barberry vulgaris preparations lasts for 10 days:

Table 15

The Course of treatment	The number of thrombocytes in blood			
	Before giving the drug	5	10	15
А				
1 2	120 x10^9/л 140 x10^9/л	140 x10^9/л 200 x10^9/л	160 x10^9/л 260 x10^9/л	210 x10^9/л 280 x10^9/л
Б				
3 4 5 6	80 x10^9/л 140 x10^9/л 106 x10^9/л 90x10^9/л	120 x10^9/л 208 x10^9/л 126 x10^9/л 120 x10^9/л	160 x10^9/л 260 x10^9/л 140 x10^9/л 140 x10^9/л	200 x10^9/л 260 x10^9/л 160 x10^9/л 200 x10^9/л

Thus, in patients with liver diseases preparations of barberry vulgaris have also a stimulant effect on thrombocytopoiesis. At the same time it was noted that the effect of a decoction of barberry vulgaris root is more manifested in comparison with other preparations

CHAPTER V. INFLUENCE OF BARBERRY VULGARIS PREPARATIONS ON THE FUNCTIONAL STATE OF THROMBOCYTES AND CAPILLARY BLOOD CLOTTING TIME

V.1. The effect of barberry preparations on adhesive-aggregation activity and thrombocytes' disaggregation in patients with ITP and symptomatic thrombocytopenia

Aggregation ability proved to be one from the numerous important hemostatic functions of thrombocytes because manifested in the first phase of blood coagulation, it serves as a trigger for the blood coagulation process (18,57,38).

The functional properties of platelets, in particular their aggregation, play a leading role among the factors determining the state of microcirculation. We tried to study the effect of barberry preparations on the adhesive-aggregation function in patients with ITP and symptomatic thrombocytopenia.

The adhesive-aggregation activity of the drugs was studied among the 40 patients, 20 of them were with ITP, 20 ones with symptomatic thrombocytopenia.

Indicators of the adhesive-aggregation function of thrombocytes in patients with ITP and symptomatic thrombocytopenia were studied by comparing the data obtained with the initial data from patients before taking this drug.

In patients with ITP, adhesive activity before administration of berberine bisulfate constituted h5-22%, h10-37%, after 5 days after taking the drug it increased to h5-37%, h10-58%; after 10 days it constituted h5 -50%, h10 -71%; after 15 days the adhesive function of thrombocytes slightly decreased: h5-46%, h10-64% (see Table 16).

Before giving a decoction of barberry root, the adhesive activity in patients with ITP was h5-20%, h10-43%; 5, 10, 15 days after taking the drug, activity indicators increased and amounted to h5-42%, h10 -62%, respectively; h5- 61%, h10-73%; h5-44%, h10-60% (P<0.01) (Table 16).

Our research results demonstrated an increase in thrombocytes' adhesive activity while taking barberry preparations (after 5-th and 10-th days), and on the 15-th day this activity slightly decreased remaining 70% higher than the initial level. Thus, we can conclude that taking barberry preparations in patients with ITP results into an increase in adhesive blood platelets' aggregation activity.

In patients with symptomatic thrombocytopenia, before administration of berberine bisulfate, the adhesive activity was on average h5 -23%, h10-35%; 5, 10 and 15 days later, after taking the drug, this activity changed significantly towards an increase: h5- 43%, hH10-63%, h5-51%, h10-72%, h5-46%, h10- 61% according to days of observation (P. < 0.001) (Table 16).

Table 16

INFLUENCE OF BARBERRY VULGARIS PREPARATIONS ON ADHESIVE FUNCTION OF THROMBOCYTES IN PATIENTS WITH ITP (A) AND SYMPTOMATIC THROMBOCYTOPENIA (B)

Groups of patients	Statistical data	Before drug administration		Observation days after drug administration					
				5		10		15	
A	M+m	22+1	37+	37+3 x	58+3	50+3 x	71+3 x	46+2 x	64
		20+2	2	42+4 x	x	51+4 x	73+4 x	44+3 x	+3
			41+	168	61+3	227	192	209	x
	%	100	4	210	x	255	178	220	60
				5.0	158	9.0	8,5	6,0	+2
	T		100	5.0	149	7.0	6,0	6,0	x
					5.0				17
					3.5				3

									146 7, 0 4, 3
B	M+m % t	23+2 25+1 100	35+ 3 37+ 2 100	43+3 x 42+22 x 187 268 5.0 6.8	63+4 x 82+2 x 180 167 7.0 9.0	51+3 x 52+14 x 221 208 7.0 13.0	72+4 x 77+25 x 206 180 7,0 13,0	46+3 x 45+11 x 200 168 5,0 13,0	61 +4 x 62 +2 x 17 4 5, 0 9, 0

Before taking a decoction of barberry root adhesive activity in patients constituted h5-25%, h10-37%; 5 days later after taking the drug its activity was h5-62%; after 10 days - h5-52%, h 10-77%; after 15 days - h5-45%, h10-62%.

The platelet aggregation function in patients with symptomatic thrombocytopenia before taking berberine bisulfate averaged hH-29%, hM-40%; 5 days later after taking the drug, this activity increased to hn-47%, hm-59%; after 10 days it constituted hH-51%, hM-67%; after 15 days it slightly decreased and amounted to hH-4 I%, hM-64%.

Patients taking a decoction of barberry root demonstrated the following: before administering the drug the aggregation activity constituted hH-29%, hM-52%; 5, 10 and 15 days later after taking the drug this activity was hH-53%, hM-72%; hH-55%,

hM-78%; hH-43%, hM -69% according to the days of observation (P<0.0I) (Table 17).

Summarizing our observations, we can conclude that the adhesive-aggregation activity of thrombocytes in patients with symptomatic thrombocytopenia under the influence of barberry preparations increases significantly during all days of observation.

Table 17

INFLUENCE OF BARBERRY VULGARIS PREPARATIONS ON THROMBOCYTES' AGGREGATION ACTIVITY IN PATIENTS WITH ITP (A) AND SYMPTOMATIC THROMBOCYTOPENIA (B)

Groups of patients	Statistical data	Before drug administration		Observation days after drug administration					
				5		10		15	
А	M+m % T	27+2 29+1 100 100	52+2 46+2 100 100	50+2 x 41+2 x 185 162 11,0 4,5	73+3 x 59+2 x 140 128 3,5 4,0	49+1 x 51+2 x 181 140 11,0 10,0	76+2 x 67+2 x 146 146 5,0 7,0	56+2 x 41+0,5 x 193 141 14,0 12,0	79+ 13 x 64+ 2 x 152 139 4,5 6,0
Б	M+m % t	29+2 29+0,5 100 100	51+3 52+2 100 100	46+3 x 53+4 x 159 183 3,0 6,0	70+4 x 72+3 x 137 138 4,0 5,0	50+3 x 55+4 x 172 190 4,0 6,0	74+2 x 78+2 x 145 150 5,0 9,0	48+2 x 43+13 x 166 148 4,0 4,0	68+ 3 x 69+ 1 x 133 133 4,0 8,5

Having approved the fact that barberry preparations play a significant role in the adhesive-aggregation function of thrombocytes, we decided to investigate the possible effect of the same preparations on blood platelets' disaggregation in patients with ITP and symptomatic thrombocytopenia.

In ADP-induced aggregation in patients with ITP and symptomatic thrombocytopenia the disaggregation process changed as follows: in patients with ITP before taking berberine bisulfate it constituted hD-70%; after 5, 10 and 15 days disaggregation constituted hD-46%, hD-32%, hD-30%, respectively during the days of observation (data presented in relation to the initial value taken as 100%) (P<0.01).

In patients with ITP before taking a decoction of barberry root the disaggregation process constituted hD-54.%; on the 5-th, 10- th and 15-th days after taking the drug, as can be seen from Table 18, a decrease in the disaggregation process was noted, and the decrease in the disaggregation process was observed at the same level (hD-32%, hD-29%, hD-30%, respectively, during the days of observation)

Table 18

INFLUENCE OF BARBERRY VULGARIS PREPARATIONS ON THE PROCESS OF THROMBOCYTES' DISAGGREGATION IN PATIENTS WITH IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP)

Preparations	Statistical data	Before drug administration	Observation days after drug administration		
			5	10	15
Barberine bisulfate	M+m % T P< N = 10	70+5 100	46+4 66 4,0 0,05	32+4 46 14,0 0,001	30+2 433 8,0 0,001

Decoction of barberry vulgaris root	M+m % T P< N =10	54+6 100	32+4 59 3,0 0,05	29+3 54 4,0 0,01	30+3 56 3,0 0,05

Table 19

INFLUENCE OF BARBERRY VULGARIS PREPARATIONS ON THE PROCESS OF THROMBOCYTES' DISAGGREGATION IN PATIENTS WITH SYMPTOMATIC THROMBOCYTOPENIA

Preparations	Statistical data	Before drug administration	Observation days after drug administration		
			5	10	15
Barberine bisulfate	M+m % T P< N = 10	63+4 100	39+5 62 4,0 0,01	27+3 43 7,0 0,001	21+2 33 9,5 0,001
Decoction of barberry vulgaris root	M+m % T P< N =10	61+3 100	31+4 51 6,0 0,001	21+0,9 34 13,0 0,001	27+1 44 11,0 0,001

After 15 days of observation, an increase in the degree of aggregation, an increase in the degree of adhesiveness and a decrease in the disaggregation process were observed. In our opinion, possible mechanism of action of barberry preparations aimed to the increasing the functional activity of blood platelets is explained by the fact that under the influence of barberry preparations in the blood the number of

“young” forms of thrombocytes increases, the increase in the latter process naturally results into an increase in the functional activity of platelets (22,38,57).

V. 2. The effect of barberry vulgaris preparations on the primary bleeding time and on the clotting time of capillary blood in patients with idiopathic thrombocytopenic purpura and symptomatic thrombocytopenia

As we noted in the literature review, a decrease in the number of platelets as well as an impairment of their function result into an prolongation of the primary bleeding time and blood clotting disorder.

Based on the above-described phenomena, we decided to study the effect of barberry preparations on the time of primary bleeding and capillary blood coagulation in the patients under our observation.

40 patients were examined, 20 of them were with ITP, 20 were with symptomatic thrombocytopenia.

Before taking berberine bisulfate in patients with ITP the time of primary bleeding constituted 675"+120 (100%); after 5 days - 577"+101 (85%), after 10 days - 257"+33 (38%), after 15 days the time of primary bleeding was further shortened and constituted 220+30" or 33% of the initial level (Table 20).

After 5 days, in absolute terms, the results obtained turned out to be unreliable, but calculating the results as a percentage gave significant differences in relation to the background values.

In patients with symptomatic thrombocytopenia before administration berberane bisulfate the average time of primary bleeding constituted 244.4+13" (100%); 5, 10, 15 days later after taking the drug - 166+15" (68%), 95.4+14" (38%), 113.3+13" (46%) according to the days of observation (see table 20).

Table 20

INFLUENCE OF BERBERINE BISULPHATE ON THE TIME OF PRIMARY BLEEDING IN PATIENTS WITH ITP (A) AND SYMPTOMATIC THROMBOCYTOPENIA (B)

Form of thrombocytopenia	Statistical data	Before drug administration	Observation days after drug administration		
			5	10	15
A					
	M+m	675+120	577.101	257+33,0	220+30
	%	100	85	38	33
	T		0.8	3,4	3,7
	P<		0,1	0,01	0,01
	N=10				
Б					
	M+m	244.4+13	166+15	94,4+14	113,13
	%	100	68	38	46
	T		3,9	7,8	7,2
	P<		0,0	0,001	0,001
	N=10				

We noted a similar picture in patients when they were prescribed a decoction of barberry root. In patients with ITP, before taking the decoction, the time of primary bleeding constituted 602+102" (100%), 5 days later after taking the drug it was decreased up to 518+96" (46%), after 10 days it was 279+34" (46%) and after 15 days -234+3I" (39%).

INFLUENCE OF BARBERRY ROOT DECOTION ON THE TIME OF PRIMARY BLEEDING IN PATIENTS WITH ITP (A) AND SYMPTOMATIC THROMBOCYTOPENIA (B)

Form of thrombocytopenia	Statistical data	Before drug administration	Observation days after drug administration		
			5	10	15
A					
	M+m	602+102	518+96	279+34	234+31
	%	100	89	46	39
	T		0,6	3,0	3,4
	P<		0,01	0,05	0,01
	N=10				
Б		253+12	186+9		
	M+m	100	74	131+13	121+11
	%		4,4	52	48
	T		0,01	7,0	8,0
	P<			0,001	0,001
	N=10				

In patients with symptomatic thrombocytopenia, before administering barberry root decoction, the average bleeding time constituted 253+12" (100%); 5, 10, 15 days later after taking the drug, it was shortened on average to 186+9" (74%), 131+13" (52%), I2I+11 (40%) according to the days of observation (see Table 21).

The data presented above give us possibility to conclude that barberry preparations significantly decrease bleeding time in patients with ITP and symptomatic thrombocytopenia. It should be emphasized that a significant shortening of bleeding time in patients is associated with the days of maximum increase in the number of thrombocytes in the peripheral blood and an increase in their functional activity under the influence of barberry preparations, which we have repeatedly indicated above (see Chapters 3, 4, 5).

We studied the effect of barberry preparations on capillary blood coagulation in the same groups of patients.

In patients with ITP before the administration of berberine bisulfate the average capillary blood clotting timeconstituted: beginning 301+43", end - 353+44"; 5 days later after taking the drug it was: beginning - 176+37", end - 235+34"; after 10 days - beginning - 165+12", end - 221+19"; after 15 days, beginning -156+10", end - 208+14" (Table 22).

In patients with symptomatic thrombocytopenia before giving berberine bisulfate the blood clotting time was on average: beginning - 368 + 55", end 414 + 32"; after 5 days - beginning - 258+31", end - 300+33"; after 10 days - beginning - 209+12", end - 273+9"; after 15 days - beginning - 224+16", end - 281+16" (see table 22).

Thus, our observations demonstrated that during treatment with berberine bisulfate capillary blood clotting time accelerated on all observation days in patients with ITP as well as symptomatic thrombocytopenia.

Taking a decoction of barberry vulgaris also had an effect on blood clotting in patients with ITP and symptomatic thrombocytopenia. In patients with ITP, the blood clotting time before giving the drug was on average 399+43", end 445+41"; 5 days later after taking the decoction the blood clotting time was; beginning- 258+37", end - 304+33"; after 10 days, beginning - 167+11", end - 223+17"; after 15 days: beginning - 163+9", end - 276+14".

In patients with symptomatic thrombocytopenia before taking decoction of barberry root the average blood clotting time was: beginning - 253+15", end - 31+19"; 5 days later after taking the drug: beginning - 192+13", end - 258+17"; after 10 and 15 days: the beginning is 254+16", the end is 194+18" and the beginning is 153+10", the end is 200+14" according to the days of observation.

The data presented demonstrated the effect of barberry preparations on the acceleration of blood clotting time in the patients we observed. Moreover, it is very typical that the acceleration of the clotting time of capillary blood was associated with the shortening of the time of primary bleeding.

Thus, barberry preparations, increasing the number of platelets in the peripheral blood, result into the shortening of the time of primary bleeding and acceleration of capillary blood clotting time in patients with ITP and symptomatic thrombocytopenia

CHAPTER VI. CONCLUSION

Thrombocatopenia of various origins is a quite common disease that affects mainly people of young, working age, mainly under 40 years old (12).

The main manifestation of thrombocytopenia proved to be: bleeding of the microcerculatory type, characterized by nasal, gum, gastrointestinal, and uterine bleeding. The most dangerous are intracranial hemorrhages, which are often fatal.

The intensification of production processes, the use of new equipment, new types of energy, synthetic materials and chemical compounds in industry provokes the occurrence of thrombocytopenia. In some cases the development of thrombocytopenia is associated with the use of pesticides in agriculture.

Clinical and geographical factors can also play a causative role in the development of thrombocytopenic purpura, especially the influence of the desert and hot climate: dehydration, changes in all types of metabolism, including hypovitaminosis (12a).

In 80% of cases, patients with acute leukemia experience severe hemorrhagic syndrome which results into death in 20% of patients (31, 32).

For the treatment of thrombocytopenia of various origins, hormonal, vasoconstrictor, hemostatic drugs, etc. are usually administered.

Glucocorticoids, immunosuppressive, immune-stimulating drugs and splenectomy are used to treat ITP. However, the drugs used do not always have a positive effect, in addition, they can result into dangerous complications. For example, taking glucocorticoids sharply increases the function of the adrenal cortex, reduces the functional state of thrombocytes (38,161); splenectomy is not always effective; effect of using immunosuppressants is only observed after 1.5-2 months. In children and

young people, cytostatic therapy can result into mutagenic effect, infertility or pathology in the fetus (24,29,67,139).

It is believed that the infusion of thrombocytes and erythrocytes often leads to allosensitization of patients, increasing the risk of infection of patients with viruses B and C, cytomegaloviruses and AIDS (25,156).

The use of vasoconstrictor and hemostatic drugs gives a short-term effect.

Consequently, the presented literature data indicate that there are no specific agents that stimulate thrombocytopoiesis. Therefore, the search for new most effective specific agents that regulate thrombocytopoiesis is topical and justified.

In this regard, the search for agents capable of stimulating thromboitopoiesis we conducted among herbal preparations. This is explained that they do not have a multiple negative impact on human organism. The flora of Uzbekistan is rich in medicinal plants, including of which the family of the genus Berberidacral takes a large place.

Information about the healing properties of barberry was known in ancient times. Barberry berries were used as a drink against the thirst, for heart disease, stomach ulcers and as a choleretic agent. A decoction of the roots of barberry was used to cure bleeding from the lower part of the body.

At present time the drug from barberry, berberine bisulfate, is used as a choleretic agent for hepatitis, hepato-cholecystitis and cholelithiasis. It is also used in obstetric and gynecological practice for atonic bleeding, in the postpartum period and for bleeding associated with inflammatory processes.

The studied drug contains mainly an alkaloid - berberine bisulfate, which is produced by Batumi Chemical Pharmaceutical Plant. According to its chemical structure it belongs to isoquinoline derivatives and is a quaternary amino base. For medical purposes the drug is available in the form of sulfate salt (bisulfate). There are isolated reports that berberine bisulfate in experimental dogs caused an increase in the number of thrombocytes in the peripheral blood (38).

We set the task to study the effect of barberry preparations on thrombocytopoiesis with a perspective to their possible use as stimulators of thrombocytopoiesis.

To solve this problem, experimental and clinical studies were conducted to study the role of drugs from barberry vulgaris on thrombocytopoiesis.

Experimental follow-up studies of barberry preparations were carried out on 230 white outbred rats. Clinical observations on 180 patients with thrombocytopenia of various origins were carried out.

Experiments have demonstrated that barberry preparations with a single intraperitoneal injection significantly ($P<0.001$) increase the number of thrombocytes in the peripheral blood and enhance the thrombocatopoietic activity of the blood serum. The administration of the same drugs also demonstrate a stimulating effect on the number of bone marrow megakaryocytes. At the same time, a megakaryocytogram study showed an increase in functioning megakaryocytes due to more active forms of the latter, i.e. polychromatophilic and basophilic forms. For example, an increase in the number of thrombopathies in rats was noted on the 3rd day after the administration of berberine bpsulfate from 306x109/l to 883x109/l (288.5%) and after the administration of a decoction barberry root - from 306x109/l to 830x109/l (271%). The noted thrombocytes'-stimulating effect lasted for 10 days. A significant increase in the number of blood platelets in the peripheral blood after the administration of barberry preparations was accompanied by an increase in the thrombocytopoietic function of the bone marrow, which was expressed in an increase in the number of megakaryocytes in the bone marrow: with the introduction of berberine bisulfate, their number increased from 87.4 (100%) to 176.0 (201 %), with the introduction of barberry root decoction - from 87.4 (100%) to 140.0 (161%) ($P<0.001$).

It is known that an increase in the number of thrombocytes in the peripheral blood is preceded by the appearance of an endogenous factor - thrombocytopoietin (65). Have being studying the mechanism of stimulation of thrombocytopoiesis under the influence of barberry preparations we investigated the thrombocytopoietic activity

of blood serum by the severity of stimulation of thrombocytopoiesis caused by the administration of donor serum to recipients.

Administration of donor blood serum activated by berberine bisulfate caused a thrombocytes'-stimulating effect in recipient rats, although this effect was less manifested compared to the effect of the administered drug. For example, the number of blood platelets increased from 304.0x109/l to 676.0x109/l (222.2%) on the 3rd day of observation. The number of megakaryocytes also tended to increase; their maximum increase was noted after 24 hours and constituted 210.5% compared to the initial level.

After administration of serum from donors who received a decoction of barberry root the maximum increase in the number of thrombocytes was noted after 3 days and amounted to 250% (the values before the administration of serum were taken as 100%). In the same recipient rats, the maximum increase in the number of megakaryocytes from 87.4 to 179.0 (204%) was observed within 24 hours. In control groups of rats after administration of serum from donors who received physiological sodium chloride solution the level of thrombocytes in the peripheral blood and the number of megakaryocytes in the bone marrow did not change.

Our results give reason to conclude that stimulation of thrombocytopoiesis by preparations of barberry is carried out as a result of an increase in thrombocytopoietic activity of blood serum, confirmed by stimulation of the bone marrow, expressed by a significant increase in the number of megakaryocytes in the bone marrow, an increase in the number of thrombocytes in the peripheral blood of rats.

Thus, based on the obtained experimental data, we believe that stimulation of thrombocytopoiesis with drugs from barberry is mediated through thrombocytopoietins, which, according to the classification of A.A. Markosyan (55,65), should be classified as long-acting thrombocytopoietins, since they stimulate the thrombocytopoietic function of the bone marrow.

Based on the fact that specific humoral activators, thrombocytopoietins, which determine the intensity of the thrombocytonoetic function of the bone marrow (55), play an important role in the regulation of thrombocytopoiesis, we made an attempt

to study the effect of serum from patients with thrombocytopenia before and after the administration of barberry preparations.

To reveal thrombocytopoietic activity, that is to determine the thrombocytopoietic factor, we used a biological method in our work, i.e. injection of blood serum from patients who took barberry preparations to experimental animals (white rats) at the rate of 1 ml/100 g of rat body weight.

The thrombocytopoietic activity of the material was assessed by the degree of increase in the number of thrombocytes in the peripheral blood of the recipient animal over 30%, as it was firmly established earlier (27, 35).

Serum from patients with thrombocytopenia was injected intraperitoneally into recipient rats twice (before the administration of the study drug and 5 days later after the patients took it, that is, on the eve of the maximum increase in the number of thrombocytes in donors).

The control group of animals was injected with blood serum from healthy people and saline in a similar way.

In the experimental group of animals, the number of thrombocytes before the administration of serum from a patient who had not yet received berberine bisulfate constituted 314.0x109/l; a day later after the administration of this serum their increase constituted only 23%, that is, thrombocytopoietic activity in patients with thrombocytopenia before the drug was prescribed was low. The same rat group was again injected with the patient's serum, but obtained after he had taken berberine bisulfate for 5 days; a maximum increase in the number of blood platelets was noted after 3 days (before the introduction of the serum - 335.0x109/l (100%), at the time of the study - 730, 0x109/l (218%).

Similar changes in the content of blood platelets in the peripheral blood of recipient rats were noted with the introduction of blood serum from donor patients who received a decoction of barberry root for 5 days. So, for example, if before the administration of serum the thrombocytes' count constituted 324.0x109/l (100%), then 3 days later after its administration it was 750.0x109/l (231%).

To confirm the phenomenon of the thrombocytopoietic activity of the serum of patients who received barberry preparations, we studied the effect of the serum of practically healthy people. At the same time, the absence of thrombocytes'-stimulating effect of the serum of healthy people was established (before the administration of the serum, the number of blood platelets constituted 388.0x109/l (100%); after administration, 3 days later - 400.0x109/l (103%).

Consequently, the data we obtained through the use of a biological sample give us a possibility to suggest that thrombocytopoietins play a role in the mechanism of the thrombocytes'-stimulating effect of barberry preparations. The latter turned out to be quite active in the blood serum of patients receiving these drugs.

Having experimentally established the fact of an increase in the number of platelets in peripheral blood under the influence of barberry preparations, we decided to study the effect of the same drugs on patients with thrombocytopenia of various origin, since the basis of this disease proved to be an impairment of thrombocytopoiesis or an impairment of megakaryocyte-thrombocytes system of the bone marrow.

In the clinic, the effect of barberry preparations was studied in 180 patients with thrombocytopenia of various origin; the control group included 40 patients who received treatment with traditional drugs (without barberry preparations).

Among the 180 patients observed, there were 67 with ITP, 33 with hereditary hemolytic anemia, 19 with polydeficiency anemia with symptomatic thrombocytopenia, 13 with hypoplastic anemia, 17 leukemias, 16 malignant lymphomas and 15 with liver disease. The results of clinical observation indicate that after taking berberine bisulfate patients with ITP experienced an increase in thrombocytes' count by 43, 68 and 87 percent, respectively, at 5, 10, 15 days of observation. After patients in the same group took a decoction of barberry root, the increase in the number of platelets was 27%, 52%, 87%, respectively, on the day of observation.

In the group of patients treated with barberry preparations, along with traditional drugs, the number of blood platelets increased by 41%, 67%, 78%, respectively during the same period of the study.

Analysis of thrombocytograms demonstrated that after taking barberry preparations the increase in the number of thrombocytes occurred due to the most active forms of platelets, which are young and mature forms.

In patients with hereditary hemolytic anemia accompanied by symptomatic thrombocytopenia, after taking berberine bisulfate the number of thrombocytes increased by 34%, 49%, 56% according to the days of observation; the increase in the number of blood platelets after taking barberry root decoction was practically no different from the effect noted when taking berberine bisulfate.

In patients with polydeficiency anemia with symptomatic thrombocytopenia taking berberine bisulfate increased the thrombocytes' count by 39%, 50%, 59% and in the control group of patients who received etiopathogenetic treatment (without taking berberine bisulfate) the increase in blood platelet count constituted 25%, 41.6%, 41.6% respectively of the observation day.

Analysis of the data obtained in this group of patients showed that while treating patients with etiopathogenetic therapy including addition of berberine bisulfate the number of blood platelets in the peripheral blood increased much faster and in the early stages, which clinicians must take into account when planning treatment for such patients.

The group of patients with hematopoietic depression consisted of 13 patients with hypoplastic anemia, I7 with leukemia. Taking berberine bisulfate by patients resulted into an increase in the number of thrombocytes by 65%, 95%, 73%, respectively on the day of observation, a decoction of barberry root - by 93%, 251.7%, 262%, respectively on the day of observation.

In our observations such a significant increase in the number of thrombocytes indicates that even with such a pathology, barberry preparations have a fairly clear stimulating effect on thrombocytopoiesis. At the same time, the most clear effect was observed in patients taking a decoction of barberry root.

Taking berberine bisulfate by patients with leukemia against the background of cytostatic therapy resulted into an increase in the number of platelets by 30%; the increased value was maintained at this level on all days of observation. And in the control group of patients who took cytostatic therapy with hemostatic drugs, but without berberine bisulfate, the number of thrombocytes tended to decrease and constituted 83.6%, 69.9%, 94% of the initial level.

Analysis of the data obtained from patients with leukemia suggests that when treating this category of patients the drug berberine bisulfate should be prescribed to correct thrombocytopenia condition and prevent bleeding.

Our studies of the effect of berberine bisulfate on patients with malignant lymphomas demonstrated that, despite the fact that they were subjected to chemoradiotherapy, the number of thrombocytes increased more than 2 times (213%, 206%, 263%) according to the days of observation; in the control group (101.6%, 116%, 128%) according to the days of observation. This gives us reason to recommend widely berberine bisulfate to patients with malignant lymphomas along with radiation and chemotherapy.

Data obtained on the effect of barberry preparations in patients with liver diseases accompanied by thrombocytopenia in whom there was a significant increase in the content of blood platelets in the peripheral blood (from 37% on the 5th day to 80% on the 15th day of observation) when taking berberine bisulfate in hospital conditions proved to be of a great significance. When taking barberry root decoction in ambulatory conditions the thrombocytes' count increased by 92% on the last day of observation.

These results give us possibility to recommend the clinicians to prescribe barberry preparations to patients with liver diseases accompanied by thrombocytopenia for the treatment and prevention of hemorrhagic syndrome.

Studies on the effect of barberry preparations on the adhesive-aggregation function of thrombocytes in patients with ITP and symptomatic thrombocytopenia showed the following picture: in patients with ITP, adhesive activity after taking berberine bisulfate increased by h5-34%, hI0-58%; h5 -50%, h10-71%, h5-46%, h10-

64% according to the days of observation, after taking a decoction of barberry root it was increased by h5-42%, hI0-61%, h5-51%, h10-73% , h5-44%, h10-60% according to the days of observation.

Aggregation activity of the same patients after taking berberine bisulfate increased by hH-50%, hM-73%, hH-49%, hM-76%, hH-56%, hM-79%; and after taking barberry root decoction it was increased on hH-46%, hM-70%, hH-50%, hH-74%, hM-48% hH-68% according to the days of observation.

In patients with ITP, taking berberine bisulfate resulted into a decrease of disaggregation process by 34%, 68%, 70% and taking barberry root decoction - by 68%, 71%, 71% according to the days of observation.

In addition to increasing the adhesive-aggregation function ofthrombocytes, berberine bisulfite also had a significant effect on the time of primary bleeding. In 5 days after taking the drug, the bleeding time was shortened on 80.5%, after 10 days - on 65.5%, after 15 days - on 37%, the shortening of the time of primary bleeding after taking barberry root decoction was 82% 54%, 44%, respectively on the 5-th , 10-th and 15-th days of observation.

Under the influence of berberine bisulfate, the clotting time of capillary blood accelerated: beginning - 58%, end - 67%: beginning - 50%, end - 63%, beginning - 52%, end - 59%, respectively on the 5-th , 10-th and 15-th days of observation. When taking a decoction of barberry root, the clotting time accelerated: beginning - 65%, end - 68%; beginning - 42% end - 50% beginning -41%, end -49% according to the days of observation.

In patients with symptomatic thrombocytopenia adhesive ability under the influence of berberine bisulfate increased on h5-87%, h10-80%, h5-221%, h10-206%, h5-200%, h10-147% respectively on the 5-th , 10-th and 15-th days of observation; and under the influence of a decoction of barberry root it increased on h5-68%, h10-67%, h5-208%, h10-208%, h5-80%, h10-68% according to the days of observation.

Aggregation activity in the same group of patients increased under the influence of berberine bisulfate on hH-62%, hM-28%, hH-76%, hM-46%, hH-41%,

hM-36%, respectively on the 5-th , 10-th and 15-th days of observation . At the same time of the study, thrombocytes' aggregation function increased on hH-83%, hM-38%, hH-90%, hM-50%, hH-48%, hM-33% under the influence of barberry root decoction.

Under the influence of barberry preparations disaggregation activity of thrombocytes decreased on 62%, 43%, 33% when taking berberine bisulfate, and on 59%, 54%, 56% when taking barberry root decoction according to the days of observation.

Analysis of the data obtained in the treatment of patients with ITP and symptomatic thrombocytopenia indicated that an increase in the degree of aggregation, adhesiveness and a decrease in the disaggregation process were observed during 15 days of observation under the influence of barberry preparations. Probably, possible mechanism of action of barberry preparations aimed at increasing the functional activity of thrombocytes is explained by the fact that the number of "young" forms of blood platelets increases under the influence of barberry in the blood; and an increase in the latter naturally results into an increase in the functional activity of thrombocytes.

Simultaneously with the increase in the functional activity of thrombocytes, the time of primary bleeding in these groups of patients was shortened, for example, under the influence of berberine bisulfate the time of primary bleeding was shortened on 68%, 38%, 46% according to the observation periods; under the influence of barberry root decoction the shortening of the time of primary bleeding reached 74%, 52%, 48% respectively.

Preparations of barberry resulted into acceleration of capillary blood clotting time in patients with symptomatic thrombocytopenia: beginning on 70%, end on 72%; beginning – 57%, end – 67%; beginning – 61, end – 69%; under the influence of berberine bisulfate, the beginning – on 76%, the end - 81%; beginning – 61%, end – 61%; beginning – 60%; end – 63% under the influence of barberry root decoction according to the days of observation.

Significant improvement in the general condition of the patients was noted in parallel with the normalization of platelet hemostasis: the bleeding was stopped, bruises were resolved, appetite was increased and the patients became more active.

In order to determine the duration of the achieved effect 10 days later after stopping treatment with barberry preparations, a control study was carried out on the thrombocytes' content in the peripheral blood of patients. It was found that the patients (the majority of the examined patients) maintained the good health achieved at the end of the course of treatment, but the number of thrombocytes was reduced compared to the indicators noted at the end of the course of treatment. In this regard, it is advisable to treat patients with ITP and symptomatic thrombocytopenia of various origins with berberine bisulfate and barberry root decoction in 15-day courses with a break of 10 days.

Therefore, summarizing our observations, we can conclude that barberry preparations in patients with ITP and thrombocytopenia of various origins results into a significant increase in the number of platelets in the peripheral blood, shortening the time of primary bleeding, accelerating the clotting time of capillary blood, increasing the adhesive-aggregation function of platelets, enhancing thrombocytopoietic activity of patients' blood serum. It should be especially emphasized that during the treatment of patients, as well as during the fixed observation periods, not a single case of negative effects of barberry preparations was noted.

CONCLUSIONS

Preparations of barberry - berberine bisulfate 0.1% solution in a dose of 1 ml/kg with a single intraperitoneal injection and a decoction of barberry root 1 ml/100 g of rat weight resulted into the increase in the number of thrombocytes in the peripheral blood in intact rats.

Thrombocytes'-stimulating effect of the studied drugs was evident, it was confirmed by an increase in the number of megakaryocytes in the bone marrow of rats as well as an increase in the thrombocytopoietic activity of the blood serum of rats and patients.

Taking berberine bisulfate at a dose of 5 mg 3 times a day for 15 days increased the number of thrombocytes in the peripheral blood of patients with ITP and thrombocytopenia of various origins; decoction of barberry root, 1 tablespoon 3 times a day for 15 days resulted into the increase in the number of platelets in the same patients.

Barberry preparations led to an increase in the adhesive-aggregation function of platelets and a decrease in their disaggregation in patients with ITP and symptomatic thrombocytopenia.

Barberry preparations shorten the time of primary bleeding, accelerate capillary blood clotting in patients with ITP and symptomatic thrombocytopenia.

Barberry preparations stimulate thrombocytopoiesis while patients are taking cytostatic drugs and radiation therapy.

The use of barberry preparations does not impair the function of vital organs and can be recommended as a stimulator of thrombocytopoiesis due to their pharmacological properties.

PRACTICAL RECOMMENDATIONS

I. Barberry preparations (berberine bisulfate and decoction of barberry root) can be recommended as a remedy with thrombocytopoietic action and normalizing the thrombocytes' component of hemostasis in patients with ITP.

2. Along with etiopathogenetic therapy patients with symptomatic thrombocytopenia are advisable to prescribe preparations of barberry.

3. In order to prevent hemorrhagic complications in patients with ITP and thrombocytopenia of various origins, it is advisable to prescribe barberry preparations on an out-patient basis in courses lasting 10-15 days.

4. In order to correct thrombocytopenia and prevent hemorrhagic complications, it is advisable to prescribe barberry preparations to patients with malignant lymphomas and leukemia.

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YUSUPOVA SH.Q., UMURZAKOVA R.Z.

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Muharrir: Maxmudov A.
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Manzil: Andijon viloyati, Andijon tumani, Oq Yor QFY, Sh.Umarov 78 uy.

Telefon: +99897 580-64-54

e-mail: kafolattafakkur@gmail.com