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The copper-containing proteins and their effect on metabolism

In the paper review of the literature on the role of copper in the body is presented. The main content of the study is the analysis of the participation of copper in protein, carbohydrate and fat metabolism. Based on the analysis of literature sources it is shown that copper is a part of many vital proteins and enzymes that influence the development of tissues and cells of the body. The article contains the elucidation of the features of the participation of protein-transporters in the transport of copper through the plasma membrane into intracellular organelles and from the cytosol into the bloodstream. The participation of copper in the metabolism depends on its physic-chemical properties. In the literature review the features of proteins that control copper hemodynamics and participate in copper-dependent signaling are clarified. The characteristic features of copper included in the composition of many enzymes are distinguished and described. It is shown that copper plays an important role in ensuring normal growth and maintaining health. It is indicated that both deficiency and excess of copper in the body lead to various diseases. The conclusion is that the biological effect of copper shows through communication with proteins, forming complexes with high biological activity.

Key words: copper, metabolism, ceruloplasmin, copper-containing enzymes, deficiency and excess of copper.

Copper is an important element of life, it participates in many physiological processes necessary for such fundamental processes as respiration, energy synthesis, elimination of free radicals, formation of connective tissue, metabolism, maturation of the extracellular matrix of neuropeptides, neuroendocrine signaling and other processes [1].

Metabolism is a set of chemical reactions that occur in a living organism to sustain life. These processes allow living organisms to grow and multiply, maintain their structures and respond to environmental influences [2]. Metabolism in a broad sense is a natural, necessary unity of contradictory processes of changing inorganic substances into living matter and living into non-living, realized through assimilation and dissimilation. Metabolic disorders inhibit the work of the hormonal, immune, digestive and nervous systems, which leads to the development of chronic metabolic injuries [3].

Copper plays an important metabolic role, and copper compounds affect the course of fat, carbohydrate and protein metabolism of all living organisms, starting from the simple cell. Directly or indirectly, copper is involved in most metabolic processes and is their main regulator [4].

The involvement of copper in the metabolism depends on its physicochemical properties. First, copper compounds react with biopolymers and form stable complexes more strongly than many other metals. Secondly, they possess properties as catalysts, which are enhanced by binding to a protein molecule. Thirdly, copper ions easily release or accept one electron, which makes copper both a donor and an electron acceptor [5].

Copper compounds actively interact with amino acids, nucleotides, nucleic acids and proteins, forming stable complexes with high biological activity. Particularly pronounced is the participation of copper in maintaining the optimal level and consistency of metabolic processes in the tissues of the reproductive organs, nervous system, organs of sight and hearing, in phospholipid biosynthesis, maintaining osteoblast activity, formation of elastic vascular tissue, skin and hair pigments, and skeletal muscle contraction. Consequently, copper is involved in the synthesis of many essential and important proteins and enzymes, thereby having a significant impact on the development of tissues and cells of the whole organism [6].

Copper expresses its biological effect through its association with proteins. Currently, such copper compounds as caeruloplasmin, placentocuprein, haemocuprein, hepatocupreine, cuproprotein have been isolated and studied. Copper binds to L-globulins and forms ceruloplasmin, which contains about 90 % of copper and is its main storage. Ceruloplasmin is a copper-containing ferro-oxidase, β-globulin, associated with 6 copper molecules. In the body, caeruloplasmin manifests itself both as an enzyme and as an antioxidant [7].

The ability of ceruloplasmin to catalyze the oxidation of catecholamines has led to the statement that this protein can control the level of adrenal gland hormone blood levels in the blood [7].

Until recently, ceruloplasmin was widely regarded as a copper-supplying protein, but observations regarding the normal metabolism of copper in patients with aceruloplasminemia do not affect this judgment.

Copper deficiency reduces the activity of ceruloplasmin in infants and leads to the development of anemia [8].

Copper is involved in the formation of the most important connective tissue proteins — collagen and elastin, which affect the synthesis of skin pigments. By participating in the synthesis of collagen, necessary for the formation of the skeletal framework proteins, copper ensures bone health. The lack of copper, which is part of lysyl oxidase, necessary for the formation of covalent crosslinks between the polypeptide chains of collagen and elastin, can cause defects in the formation of connective tissue, including the cardiovascular system and skeleton [9].

Proteins metallothionein (MT) and COMMD1 (copper metabolism (Murr1) domain containing 1) control copper hemodynamics and participate in copper-dependent signaling.

Metallothionein (MT) — is a low molecular weight protein, rich in cysteine, capable of binding metal ions. MT is involved in maintaining the cellular homeostasis of copper and performs the function of intracellular copper depot. It can also block absorption, protecting the body from toxic levels of metal [10].

Studies of copper metabolism show that in some periods of a person's life the level of copper in the body noticeably increases, for example, during fetal development [11]. In enterocytes, hepatocytes and some other cells of the fetus and newborns, the concentration of metallothionein is much higher, and the intensity of ceruloplasmin synthesis is less than in adults. This explains hypocupremia and the accumulation of copper in the tissues during this period of development, which are caused in the newborn by the immaturity of the biliary system, low synthesis of ceruloplasmin, and therefore copper is associated with metallothionein [12].

COMMD1 (copper metabolism (Murr1) domain containing 1) is a multifunctional protein, the most important function of which is to participate in the maintenance of copper homeostasis in the cell. This protein plays a role in the removal of copper from the cell, as evidenced by the results of the short-lived COMMD1 knockdown in HEK293 cells, leading to an increase in the level of intracellular copper [13].

Some proteins, such as CTR1 (high affinity copper uptake), CTR2 (low-affinity copper uptake), AP-7 (also known as Menkes' protein; copper-transporting P-type ATPase), ATP7B (Wilson disease protein, copper-transporting P-type ATPase) and others are involved in the intracellular movement of copper [14].

The CTR1 protein (encoded by the SLC31A1 gene) is a high affinity transmembrane importer of copper, which provides the main route for copper to enter cells. The CTR1 protein carries out the delivery of copper ions in the oxidation state of Cu (I), but at the same time most of the food copper remains in the Cu (II) state, i.e. to get inside the cell copper must be reduced. The extracellular ligand delivering copper to CTR1, as well as the mechanism of copper reducing reaction, remains unexplored. The CTR2 protein (encoded by the SLC31A2 gene) is a low-affinity transporter that transports copper through the membrane. In mammals, CTR2 protein is found in intracellular membranes, such as vacuole, vesicle, endosome and lysosome membranes, but its localization may vary depending on cell type and copper content [15]. The volume of copper transported through the plasma membrane depends on its extracellular concentration [16].

J.M. Arguello et al. (2007) found that ATP7A and ATP7B proteins belonging to the ATPase family excrete copper from cells. They use the energy of ATP hydrolysis to transport copper from the cytosol across cell membranes, and thus cause a decrease in copper concentration in it [17]. Excretion of copper from the body can occur through bile (in the case of ATP7B), and it can also be released into the bloodstream for subsequent redistribution in the body (in the case of ATP7A).

In studies of A. Gupta and S. Lutsenko (2009), copper ATPase has been shown to deliver copper to various secretory enzymes, such as ceruloplasmin, peptidylglycine alpha-amidating monooxygenase, and others [18]. The process of copper delivery and its incorporation into the active center of the enzyme is not fully understood. However, it has been shown that apoceruloplasmin receives copper from ATP7B, and copper released by ATPase is incorporated into the active center of the fully formed enzyme by free diffusion [19].

Z. Qin, et al. (2006) found out that in the case of the Cu^{2+}/Zn^{2+} — superoxide dismutase enzyme receiving copper from ATP7A, the interaction between the transporter and the acceptor can activate the release of copper from the ATPase and cause its subsequent incorporation into the active center of the acceptor protein [20].

The main biochemical function of copper in the body is participation in enzymatic reactions as an activator or as part of copper-containing enzymes [21].

It is well known that copper is a part of many enzymes, such as amine oxidase, dopamine beta-hydroxylase, dopamine beta-monooxygenase superoxide dismutase, diamine oxidase, histaminase, monoamine oxidase, lysyl oxidase, ferroxidase, cytochrome c oxidase, tyrosinase, peptidylglycine alpha-

amidating monooxygenase, hormones and vitamins. Different types of metabolism are associated with these enzymes [22], allowing us to study some of them.

AOC3 (amine oxidase, copper-containing 3), which is distributed as vascular adhesion protein-1, belongs to copper-containing enzymes, it is secreted by vascular smooth muscle cells, adipocytes, and endothelial cells. This enzyme is a multifunctional molecule that exhibits both adhesive and enzymatic properties. Vascular adhesion protein-1 is involved in the delivery of leukocytes to the site of inflammation, the development of rheumatoid arthritis, psoriasis, systemic sclerosis, respiratory diseases, diabetes and its vascular complications [23].

Superoxide dismutase (SOD) is a family of proteins that perform the process of dismutation of a superoxide radical, forming hydrogen peroxide and molecular oxygen. SOD is an important component of the body's antioxidant defense, neutralizing the constantly formed reactive oxygen species (ROS). It is known that Drosophila, as well as microorganisms devoid of SOD, are more sensitive to the action of ROS [24]. The following protein isoforms were identified in mammals: superoxide dismutase (SOD1), superoxide dismutase 2, mitochondrial (SOD2, manganese-dependent superoxide dismutase) and extracellular superoxide dismutase [Cu–Zn] (SOD3).

SOD1 is a very stable homodimeric protein with a molecular weight of 32 kDa. In the initial superoxide dismutase description, J.D. Crapo, T. Oury, et al. (1992) showed that SOD1 contains copper atoms, which are necessary for its functional activity. It is found predominantly in the cytoplasm of cells, but it has also been found in the nucleus and peroxisomes [25]. Each SOD1 monomer contains a catalytic compound of copper, as well as zinc compounds, necessary for the formation of a stable protein structure. Knockout of the SOD1 gene in mice leads to the development of chronic peripheral neuropathy, affecting primarily the axons of motor neurons in the distal extremities [16]. In the liver of rats, SOD1 was also detected in the intermembrane space of mitochondria. In addition, SOD1 is needed to maintain the functioning of neuromuscular contacts in the limbs [26].

Superoxide dismutase (SOD3) is a 135 kDa homotetramer. The SOD3 protein contains three functional domains: an N-glycosylation site that increases SOD3 solubility, a 50 % active site homologous to SOD1, and a heparin-binding domain involved in binding to heparan sulfate by proteoglycans, which occurs on the cell surface and in the extracellular space [27].

In the SOD2 enzyme, copper atoms are involved in the conversion of superoxide anions (O_2^-) to H_2O_2 and O_2. The zinc atom in this enzyme is metabolically inactive and performs a structural function. Systemic sclerosis refers to chronic autoimmune diseases of the connective tissue, it is characterized by the development of fibrous tissue in the skin, skeletal muscles, blood vessels and visceral organs. In patients with this type of pathology, there has been a manifold increase in the production of SOD 3, Cu-Zn-dependent extracellular SOD. Mutation of the gene encoding Cu-Zn-SOD is most often observed during the development of amyotrophic lateral sclerosis, which is accompanied by dysphagia and dysarthria [28].

Cytochrome c oxidase is a copper-containing enzyme that is the terminal member of the electron transfer chain in all aerobic cells-complex IV of the respiratory chain. It is located on the inner membrane of the mitochondria of eukaryotes, and is also integrated into the plasma membrane of many prokaryotic cells [29]. In the active center of the protein, molecular oxygen is reduced to water. According to the results of crystallographic studies, until recently it was believed that the eukaryotic central organ contains 11 to 13 polypeptide subunits: 11 in Saccharomyces cerevisiae, 13 in mammals. However, studies conducted by Balsa and co-authors (2012) revealed that the NDUFA4 protein, previously considered a component of the NADH-dehydrogenase complex of the respiratory chain [30], is in fact a part of the complex IV. J. Carroll, I.M. Fearnley, et al. (2006) showed that no trace of NDUFA4 protein was detected in crystallographic studies of the complex IV, they suggested that the loss of this protein occurs during the purification of the protein complex in preparation for growing crystals [31].

Copper metabolism is often observed in Willebrand disease, deficiency of blood coagulation factor VIII, which is manifested by a decrease in the level of the enzyme cytochrome c oxidase in platelets. Lee's syndrome also shows a decrease in the activity of this enzyme in skeletal muscle biopsy [11].

Diamine oxidase is involved in the inactivation of histamine, the release of which occurs during allergic reactions, as well as putrescine, 1-phenylethylamine, tyrosine, tryptophan, serotonin and spermine [32]. In diseases of the gastrointestinal tract (GIT), the consumption of foods rich in histamine, or the use of diamine oxidase inhibitors, the development of histamine intolerance is observed. In case of imbalance in the production and biotransformation of histamine, allergic reactions develop. A diet with the exception of histamine is

prescribed for the treatment of such diseases. It is believed that the basis of drug allergy, for example, to nonsteroidal anti-inflammatory drugs (NSAIDs), also lies in the gene polymorphism of diamine oxidase [33].

Monoamine oxidase (MAO) is an enzyme that catabolizes monoamines through their oxidative deamination. It is important for the degradation of serotonin, the metabolism of catecholamines, such as adrenaline, noradrenaline and dopamine [34].

According to J. Turnlund (1999) lysiloxidase uses lysine and hydroxylysine found in collagen and elastin to produce the cross-links necessary for the development of connective tissues, including bones, teeth, skin, lungs, and the vascular system [34].

The defect in the synthesis of lysyl oxidase is accompanied by the appearance of the X-linked form of elastolysis-stiff skin syndrome (SSS) and Ehlers – Danlos syndrome (EDS). Indian childhood cirrhosis (ICC) refers to chronic liver disease, the outcome of which is cirrhosis, which occurs in the pediatric population (1–3 years). This process is accompanied by the deposition of hyaline (Mallory body) and the accumulation of copper and zinc in the liver [35].

Ferroxidases are copper enzymes found in plasma, they are involved in the delivery of iron ions, which are the basis of such fundamental cellular processes as oxidative phosphorylation, oxygen transport, the formation of connective tissue, and many other [34].

Tyrosinase is a copper-containing enzyme that catalyzes the oxidation of phenols. Tyrosinase catalyzes the synthesis of melanin and other pigments from their precursor tyrosine. Tyrosinase catalyzes the conversion of tyrosine to dopamine and oxidizes dopamine to DOPA chinone (dihydroxyphenylalanine chinone). As part of the enzyme tyrosinase, copper is involved in the formation of melanin. Melanin is a skin and hair pigment that protects against ultraviolet radiation [36].

Genetic disorders of tyrosinase production lead to the development of albinism and vitiligo. Disturbance in the delivery of copper from chaperone ATP7A to tyrosinase occurs with the development of a genetic disease — Hermansky – Pudlak syndrome, which is accompanied by hypopigmentation of the eyelids and nystagmus. In the clinical picture of this disease, hemorrhagic diathesis, granulomatous colitis and restrictive lung fibrosis are observed [37].

Peptidyl-glycine alpha-amidating monooxygenase (PAM) is an enzyme function of which is alpha-amidation of precursors of many peptide hormones to biologically active forms. The peptidylglycine α-amidating monooxygenase enzyme contains two catalytic domains: the first, peptidylglycine alpha-hydroxylating monooxygenase (PHM), includes a copper compound and the second, peptidyl-alpha-hydroxyglycine alpha-amidating lyase (PAL). The PHM domain catalyzes the hydroxylation of glycine, which is located at the C-terminus of many inactive forms of neuropeptides [38]. PHM is involved in the post-translational modification of many important neuropeptides, including oxytocin, vasopressin, adrenocorticotropic hormone, vasoactive intestinal peptide, substance P, neuropeptide Y, cholecystokinin, gastrin and many others. PHM is a membrane-bound or vesicular protein, although it is found in blood serum. J.R. Prohaska, et al. (2006) showed that in vitro the biochemical activity of this enzyme is reduced in the tissues and blood serum of copper-deficient rats [39].

As part of various enzymes and proteins, copper, certainly has an impact on metabolism. Thus, it was found that copper affects carbohydrate metabolism, catalyzing the oxidation of glucose, delaying the breakdown of glycogen and contributing to its accumulation in the liver. It is known that more than 50 % of the energy that the body consumes is formed by the oxidation of glucose [7]. If a large amount of copper is present in the process of glucose oxidation, hyperglycemia appears in the body [40]. When a small amount of copper is present, hypoglycemia appears in the body [41].

Copper compounds inhibit adrenal hyperglycemia, help to reduce the level of lactic acid in patients with diabetes. Copper enhances the activity of some pituitary hormones. The introduction of thyroxin helps to increase copper in the blood, the removal of the thyroid gland reduces it [42].

Copper in the body of animals is in close interaction with insulin and adrenaline, affecting the metabolism and use of carbohydrates [7]. It participates in the breakdown of carbohydrates, in the synthesis of prostaglandin and helps the normal operation and activation of insulin. Prostaglandin controls various functions in the body, including cardiac muscle contraction, wound healing, blood pressure [43].

According to the research results of A.A. Lukyanova (2016), it can be assumed that the introduction of additives of copper in various forms into the organism of animals contributes to the activation of zinc cations, since zinc and copper determine the synergistic activity in the process of intermediate metabolism. Maintaining an optimal level of blood glucose is provided by an interrelated and balanced glycogenesis

process. Zinc cations are involved in this process that are part of the hormone insulin, which has a glycolytic effect [44].

Copper takes part in energy exchange (including oxidative phosphorylation and free oxidation) and influences the reproduction, growth and development of the organism. Copper plays two main roles in energy production. First, it helps with the inclusion of iron in red blood cells and prevents anemia. Secondly, it participates in the generation of energy from carbohydrates inside the cells. Copper allows you to regulate energy consumption and saturate it with all the cells of the body [37].

In addition to carbohydrate metabolism, copper acts as a regulator of the breakdown of fats. In particular, employees of the California Institute of Technology found that copper plays an important role in lipid metabolism: the more copper in the human body, the more fat is broken down [44].

The role of copper in fat metabolism has been studied in animal experiments. During one of them, scientists found that individuals with a genetic mutation, which leads to the accumulation of copper in the liver, have a greater amount of fat deposits than animals without such a mutation. In addition, lipolysis in their bodies was less active [45]. Analysis of the functions of copper during lipolysis revealed that this compound inhibits the activity of the enzyme phosphodiesterase, which contributes to the breakdown of fats. The breakdown and absorption of fat occurs mainly in the small intestine and duodenum [46].

D. Huster, S. Lutsenko (2007) established a link between copper metabolism, the cell-division cycle and cholesterol synthesis, and identified several candidate proteins that can mediate copper status and lipid metabolism. These data suggest that altered lipid metabolism may be associated with copper toxicity [47].

In addition, Burkhead et al. (2011), using animal models of Wilson disease, revealed a link between molecular pathways, including cell cycle and cholesterol metabolism, mRNA binding and nuclear receptor signaling, which primarily affect the accumulation of copper in the liver [48].

Normally, there should be enough copper in the body so that it can be included in specific apoenzymes, providing synthesis of these proteins. Almost all disorders of copper metabolism are the effect of either a deficiency of one or more of the necessary copper-containing proteins, or the fact that there is more copper in the tissues and organs than they can bind. Both the synthesis of specific copper-containing proteins and the balance of copper are regulated by genetic mechanisms [49].

A decrease in copper levels is often associated with diseases of the immune system, a decrease in the level of neutrophils, leukocytes, and antioxidant protection of the body. However, the level of serum copper and ceruloplasmin increases in various inflammatory processes, myocardial infarction, liver disease, pregnancy, etc. It is believed that these conditions can mask the copper deficiency in the body and make it difficult to diagnose [11].

Copper deficiency is accompanied by hypercholesterolemia, which is explained by a decrease in the activity of lipoprotein lipase, lecithin-cholesterol acyltransferase and many other enzymes. Hypercholesterolemia and vasopathy with copper deficiency can cause early development of atherosclerosis and coronary heart disease [50].

Copper deficiency is associated with the development of atherosclerotic dyslipidemia, metabolic syndrome, and impaired carbohydrate tolerance. Thus, in individuals with non-alcoholic fatty liver disease, there is a decrease in the level of copper, both in the liver and in the blood. A low level of copper in the diet leads to an increase in the synthesis of cholesterol and other lipids in the liver, as well as changes in the metabolic relationship during pregnancy between mother and fetus. Copper deficiency is possible in children with full parenteral or unbalanced micronutrients artificial feeding. At the same time, the deficiency of transferrin and ATP leads to the occurrence of microcytic iron deficiency anemia [51].

Most often, copper deficiency is diagnosed because of its low food intake and defects in copper absorption in the gastrointestinal tract, its transport to the cerebrospinal fluid, macrophages, etc.

Genetic disorders of copper metabolism that are associated with proteins (ATP7A and ATP7B), which are responsible for the excretion of copper from cells, are widely known. It is noted that the expression of ATP7B is observed in the liver, kidneys, eyes, epithelial cells and the central nervous system [37].

Copper, which enters the body in excess, is able to form strong bonds with sulfhydryl groups, inactivating some enzymes (alkaline phosphatase, saliva amylase, lipase). At the same time, it interacts with hormones (adrenaline) and affects the concentration of a number of vitamins (C, A, B) in organs and tissues [52].

An excess of copper in the membranes stimulates lipid oxidation, activates calcium release, violates transmembrane transfer of substances [53]. In addition, an excess of copper leads to damage to the cytoskele-

ton and membranes, including lysosomal ones, which also helps to further accumulate copper in the cells due to the violation of the lysosomal excretory function [37].

Thus, copper plays a large role in ensuring normal growth and maintaining health. The effects of copper exposure, mainly implemented through proteins and enzymes that include copper. In some cases, these disorders are the result of the disease, and in others — the cause of its occurrence. Excessive or insufficient intake of copper in the body causes various pathological disorders, including chronic inflammatory diseases, anemia, diseases of the musculoskeletal system, etc.

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Құрамында мысы бар ақуыздар және олардың метаболизмге әсері

Мақалада мыстың ағзадағы рөлі туралы әдеби жұмыстарға шолу жасалды. Зерттеудің негізгі мазмұны мыстың ақуыз, көмірсу және май алмасу үдерісіне қатысуының талдауын құрайды. Әдеби көздерді талдау негізінде мыстың ағзаның ұлпалары мен жасушаларының дамуына әсер ететін көптеген өмірлік қажетті ақуыздар мен ферменттердің құрамына кіретіні көрсетілген. Транспортер ақуыздардың мысты плазмалық мембрана арқылы жасушаішілік органеллаларға және цитозольден қан ағымына тасымалдау үдерісіне қатысуы сипатталған. Мыстың зат алмасу үдерісіне қатысуы оның физикалық-химиялық қасиеттеріне байланысты болады. Әдеби шолуда мыс гемодинамикасын бақылайтын және мыс-тәуелді сигналалингке қатысатын ақуыздардың ерекшеліктері анықталып, жазылған. Көптеген ферменттердің құрамына кіретін мыстың өзіне тән қасиеттері ерекшеленген және сипатталған. Мыстың қалыпты өсуді қамтамасыз ету және денсаулықты қолдауда үлкен рөл атқаратыны көрсетілген. Ағзадағы мыстың тапшылығы, сонымен қатар артықшылығы да әртүрлі ауруларға алып келетіндігі айтылған. Мыс өзінің биологиялық әсерін ақуыздармен байланысу арқылы жоғары биологиялық белсенділігі бар кешендер құра отырып, көрсететіні баяндалған.

Кілт сөздер: мыс, метаболизм, церулоплазмин, құрамында мысы бар ферменттер, мыстың артықшылығы мен жетіспеушілігі.

А.Е. Конкабаева, А.А. Арыстанбай, Ш.А. Муханова, Р.А. Колосов

Медьсодержащие белки и их влияние на метаболизм

В статье дан обзор литературы о роли меди в организме. Основное содержание исследования составляет анализ участия меди в белковом, углеводном и жировом обмене. На основе анализа литературных источников показано, что медь входит в состав многих жизненно необходимых белков и ферментов, оказывающих влияние на развитие тканей и клеток организма. В статье содержится выяснение особенностей участия белков-транспортеров в переносе меди через плазматическую мембрану во внутриклеточные органеллы и из цитозоля в кровоток. Участие меди в метаболизме обусловлено ее физико-химическими свойствами. В литературном обзоре выяснены особенности белков, которые контролируют гемодинамику меди и участвуют в медь-зависимом сигналинге. Выделены и описаны характерные осбенности меди, входящие в состав многих ферментов. Показано, что медь играет большую роль в обеспечении нормального роста и поддержании здоровья. Указано, что как дефицит, так и избыток меди в организме приводят к различным заболеваниям. Авторы пришли к выводу, что свое биологическое действие медь проявляет посредством связи с белками, образуя комплексы, обладающие высокой биологической активностью.

Ключевые слова: медь, метаболизм, церулоплазмин, медьсодержащие ферменты, дефицит и избыток меди.

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