Dietary food supplement

BETULIN

(Betulafarm®)

Betulafarm
Синтезировано природой

USER'S INSTRUCTION

Scope of application
It is recommended as dietary food supplement — a source of betulin.

Composition

Microcrystalline cellulose – 140 mg, birch betulin (birch bark extract) – 40 mg.

Capsule shell composition – gelatin, titanium dioxide, ferric oxide.

Directions for use – for adults: take 1 capsule per day with food during 3-4 weeks. Repeat the course, if necessary. Consult your doctor before use.

Contraindications
Idiosyncratic reaction to product ingredients, pregnancy, breast-feeding.

Size: 180 mg capsules.
Shelf-life: 2 years from the date of manufacture.

Storage conditions: store in dry place; keep out of reach of children; don't store above +25 °C.

TS 9197-002-74779358 -15

EAC

It is not a drug product.
Certificate of State Registration

RU.77.99.88.003.E.006199.05.15 dd. May 06, 2015

It is not a drug product.

"Betulin" should be sold through specialized stores or pharmacy chain shops.

Manufacturer

Vitamer LTD., Office III, 1 Orlovo-Davydovskiy Lane, Moscow, 129110,

Production address: 11 Sovkhoznaya Street, Petushki, Vladimir Region

By order of Betulafarm LTD.,
5 Lev Tolstoy Street, St. Petersburg,.

Claims to be sent to the authorized organization below:
BetulaFarm LTD., 5 Lev Tolstoy Street, St. Petersburg
Phone: 8 800 100 1738.

ADDITIONAL INFORMATION

Detailed information — on the company's web-site: www.betulin.com

Betulin (lup-20(29)-ene-3β, 28-diol) is widespread, natural compound from the triterpenes group produced from upper birch bark.

Betulin is white color powder, odorless, with weak astringent taste. It is oxygen- and sunlight-resistant, non-toxic. Water-insoluble. It is very soluble in organic solvents. High melting temperature of betulin (240-260 °C), stable chemical formula and inert properties of the molecule provide extended storage period without changing properties.

SCOPE OF APPLICATION

It is recommended as a dietary food supplement — a source of betulin. Betulin can be prescribed as a powerful prophylactic preparation at the secondary immunodeficient states of any origin, at the "chronic fatigue" syndrome and especially for prevention of different viral diseases, in particular for prevention of the acute respiratory viral infection and flu. It can be used as hepatoprotective, choleretic, antilithogenous, antioxidative, anti-inflammatory, antitumoral, hypocholesterolemic, antiviral, immunomodulator, hypolipidemic, antihypoxant, gastroprotective, neuroprotective, antimutagene agent.

BIOLOGICAL PROPERTIES AND PHARMACODYNAMICS

Biological activity of both the birch bark extract and its components has been confirmed during scientific researches in more than 40 foreign and Russian scientific centers. Efficiency in using triterpene compounds as direct regulators of activity of enzymatic systems in the human body protection has been demonstrated. Long-standing scientific researches proved the historical and evolutionary fixed function of triterpene compounds in metabolism regulation of the human cell. Betulin controls the action of enzymes in the cell of the human body by regulation of their synthesis and disintegration, as well as by influence on the activity of enzymes. The researches demonstrated the hypocholesteremic action of betulin on the model of the twin hypercholesterolemia. Betulin in a dose of 150 mg/kg reduced the cholesterol content in blood. Introduction of betulin in a dose of 10 mg/kg normalized biochemical processes at the toxic liver damage (caused by carbon tetrachloride introduction) due to modulation of enzyme systems (ALT; ALP) action. The study of gastroprotective properties of betulin on the indometacion gastric ulcer model demonstrated that in a dose of 600 mg/kg betulin renders antiulcer action reducing the number of lesions considerably. In addition, betulin has anti-inflammatory activity, causes inhibition of exudative and proliferative phases of inflammation. It has been revealed that betulin reduces penetrability of cutaneous vessels similar to dihydroquercitin (200 mg/kg) and renders capillary roborant effect (400 mg/kg). According to the international toxicological classification, betulin belongs to the 4th class of low-toxicity substances: (LD

50) of betulin is 9000 mg/kg. Betulin does not have allergenic, carcinogenic, dermatoirritative, cumulative, mutagenic, sensitizing and embryotoxic action. Studies of microbiological indexes of betulin as BAA and raw material for food industry have been carried out. It was revealed according to the test results that betulin comply with requirements of the Sanitary Regulations and Standards 2.3.2.1078-01 the "Hygienic safety requirements and the nutritional value of food products" p. 1.10.5 by the safety indexes (microbiological, content of toxic elements, pesticides and radionuclides).

The pharmacological activity of betulin is wide and well studied. This spectrum of actions is interconnected; many actions result one from the other. Main betulin properties: hepatoprotective, choleretic, antilithogenous, antioxidative, anti-inflammatory, antitumoral, hypocholesterolemic, antiviral, immunomodulator, hypolipidemic, antihypoxant, gastroprotective, neuroprotective, antimutagene. Nowadays the interest in its action just increases, as demonstrated by numerous domestic and foreign publications.

ANTIINFLAMMATORY AND IMMUNOMODULATOR ACTION OF BETULIN

Betulin activates phagocytosis significantly (nonspecific factors of immunity), activates macrophages, which begin to absorb bacteria more actively, as well as cancer cells uncontrollable by the body and cells affected by viruses.

Betulin demonstrates the apparent anti-inflammatory effect regarding to the exudation and proliferation phase. Betulin has an effect on the immune system through the cytokine network. Cytokines are soluble peptide neurotransmitters, which are messengers of intercellular interactions at the immune response. They determine a type and duration of the immune response, control proliferation of cells, hemopoiesis, inflammation, wound healing and other processes.

ANTIVIRAL ACTION OF BETULIN

It was demonstrated that betulin induces the interferon synthesis orally. The antiviral activity of betulin was ascertained regarding to viruses of the bird flu, type A flu virus, herpes simplex virus, hepatitis C, HIV-1, infectious rhinotracheitis, illness of mucous membranes, diarrhea virus. The mechanism of the betulin medioprophylactic action is related to its viricidal, interferon inducing and immunomodulatory action.

Betulin blocks a site in the virus protein molecule, which proteinase contacts with, as a result the virus is deprived a possibility to infect other cells. Betulin influences on the virus replication late stage, on the formation process of the capsid – a cone-shaped core, which jointly with internal nucleocapsid provides the correct packing of the viral genome – two molecules of the single-stranded RNA. As a result, the core and internal nucleocapsid take the wrong form preventing the maturation of a viral particle. Any failure in the viral proteolysis process leads to the loss of infectivity (virulence) by the virus. Hence, betulin prevents the adequate virus reproduction in the body.

An advantage of betulin is the fact that the amount of antiviral preparations is limited; many immunomodulators cannot be widely used in the clinical practice due to their toxicity and undesirable effects. For example, interferon preparations are characterized by their short duration of action, a necessity to use them in the initial stage of disease and high cost. The prolonged use of interferon causes anxiety and irritability, phrenoplegia and attempted suicide. Acyclovir and preparations on the basis of triazocompounds seriously impair the liver and kidneys. When treating with HIV-preparations based on blockers of reverse transcriptase and others, doctors have to condone with extremely serious complications in the course of the antiretroviral therapy due to the absence of an alternative. Betulin is not toxic and does not have side actions. Betulin is able to reduce the interferon system hyperactivity, promotes its functional activity at hyporeactivity and favors to maintain the ability of leucocytes to produce interferon.

HYPOLIPIDEMIC ACTION OF BETULIN

Betulin has hypolipidemic and hypocholesteremic action.

Atherosclerosis is a disease of arteries, which is accompanied with appearance of atherosclerotic plaques, narrowing of blood vessels and circulatory deficiency. Atherosclerosis develops in the body slowly and in a latent form. Clinical signs of atherosclerosis give evidence of serious pathology. Atherosclerosis can result in coronary artery disease, acute myocardial infarction, stroke, lesions of great vessels of extremities and abdominal cavity organ.

The atherogenesis mechanism has been well studied. The disease starts with oxidation of lipoproteins and their accumulation in vessel walls. Lipoproteins (spherical structures) consist of cholesterol, cholesterol ester and triglycerides of fat acids. Their main part is metabolized and removed by liver; therefore, failures in liver action and oxidates of cholesterol influence on formation of atherosclerotic plaques.

The endothelium of blood vessels is the most vulnerable to damages from the side of pathogens. The damage of vascular endothelium can be inflammatory and non-inflammatory character, which results in morphological changes of its cells.

The herpes group viruses can also participate in pathogenesis of atherosclerosis. It is known that the herpes simplex virus-1 infects not only nervous and epithelial tissue, but endothelia of great and minute vessels as well. Herpes simplex virus-1 and cytomegalovirus can initiate inflammatory changes in a vascular wall and become a triggering mechanism and the entrance gate for the atherosclerotic plaque development.

In the presence of betulin, there is a delay of cholesterol suction from bowels in the body, strengthening of cholesterol removal with bile and its oxidation into bile acids, suppression of synthesis of cholesterol surpluses in liver.

Betulin prevents the development of inflammatory processes in vascular walls. It has antiviral and bactericidal actions, improves the barrier functions of vascular endothelia. For example, cellular membranes of cardiac hystiocytes contain the increased amount of phospholipids, which are especially sensible to peroxidation. It is commonly supposed that degradation of membranes of cardiac hystiocytes at an ischemia in 60 % follows by nonenzymatic way with participation free radicals. Betulin as an antioxidant can promote to prevent their damage development.

HEPATOPROTECTIVE ACTION OF BETULIN

Studies of hepatoprotective action of betulin during development of acute hepatitis caused by paracetamol, carbon tetrachloride or ethanol demonstrated its high efficiency in blocking destruction processes of liver cell membranes, suppression of activity of enzyme systems and tissue

respiration, reduction of peroxidation of lipids of cellular membranes. Betulin increased synthetic processes in liver cells and restored the biligenic function. Betulin blocked the influence of carbon tetrachloride, which causes necrosis of hepatic cells, inflammatory edema and cellular infiltration. Betulin impeded the development of necrosis of hepatic cells, hepatic steatosis and accumulation of alcoholic hyaline under the influence of ethyl spirit, i.e. prevented the cirrhosis development. At chronic hepatitis betulin reduced the elevated levels of AST, ALT and LDH effectively. It has been established that betulin is able to protect cellular membranes against damaging action of xenobiotics. Prophylactic application of betulin (14 days) in a dose of 10 mg per kilogram of weight prevents the destruction of hepatocytes, inflammatory infiltration, colliquative necrosis, improves the liver biligenic function (the bilification intensity was restored on the 4th day after intoxication), protects liver zones with localization of cytochrome P-450. At that, the activity of ALT decreased for 82 %, alkaline phosphatase — for 69 %, content of triglycerides in blood — for 62 %, decrease of triglycerides in liver tissue — for 55 %. Betulin stabilizes membranes of mitochondrions (cell energy depot), preventing their damage as a result of oxidation processes, starts the natural apoptosis process not allowing the mitochondrial DNA escaping from the damaged cell and in so doing to initiate the autoimmune process (inflammation). Hence, betulin counterbalances intracellular homoeostasis at the expense of stabilizing of plasma membrane and membranes of intracellular organoids, as well as activating the main detoxicating enzyme — cytochrome P-450. The ability of betulin in conditions of hypoxia — a state accompanying the toxic liver damage — to increase the level of cytochrome P-450 in it and relative activity of monooxygenases indicates about this. Betulin as a natural hepatoprotector is effective at acute and chronic liver damages of any etiology including complicated by cholestasis. Betulin demonstrated the efficiency at viral diseases of liver (hepatitis A, B and C) as well, during chemotherapy and radiation therapy of oncologic patients, at alcohol-induced liver injuries (as a prophylactic drug), at injuries, burns, surgical operations, particularly with general anesthesia. Application of betulin in the complex therapy of hepatitis and hepatocirrhosis results in the acceleration of clinical recovery and renewal of physical working capacity. The absence of toxicity and side effects even at the prolonged application of betulin and heavy damage of liver parenchyma is an important factor of application of betulin.

ANTIOXIDANT ACTION OF BETULIN

The damage of plasma membranes and membranes of intracellular organoids (especially mitochondrions, lysosomes and the karyon shell) is the basis of all pathological processes. The cell membranes contain the increased amount of phospholipids consisting of polyunsaturated fat acids.

They are the main target for active oxygen forms.

This process is named the lipid peroxidation. Active oxygen forms are developed both at different pathologies and in the process of tissue respiration. Antioxidants are destined to neutralize their influence, in particular, vitamins and triterpenoid compounds. Antioxidants are an important link of the regulation mechanism of proliferative processes. The inhibition of liver lipid oxidation by betulin at acute toxic hepatitis was revealed. Several reactionary centers constituent in the betulin structure take part in the inhibition of oxidation. The greatest contribution belongs to the primary hydroxyl C-28-OH. This is more than a half of the efficiency of the whole betulin structure. The inhibitory action of betulin is also related to involvement of alcohol groups in the oxidation process, where the exchange of active radicals for oxyperoxy radicals takes place, the structure of which contains intramolecular hydrogen bond, which reduces their activity in reactions of continuation of chains. This results in entropy reduction during formation of an activated oxidizing complex. Phospholipids (PL) are an objective index of the body status in the norm and pathology. The dynamics of PL at ischemia and the behavior of phospholipids at prophylactic introduction of betulin have been studied. Tissues of brain, liver and kidneys have been examined to study the PL dynamics. It has been established that betulin acts by way of transmission of a radical center from the lipoprotein to the betulin hydrocarbon chain with its subsequent movement in the direction of the polar part of an inhibitor molecule. It has been illustrated that betulin molecules restore the structure of damaged biological membranes under the “patch the holes” principle.

Antiadipositas action of betulin:

An article of scientists in the “Cell Metabolism” journal dd. 01.2011 caused the roaring interest to a well known and seemingly to the well studied product — betulin. A dream of the humanity “How to lose weight lying on a sofa!” comes true. An unexpectedness of this discovery is that the availability of betulin in the body changes the mechanism of fat digestion by liver, which results in the cholesterol decline in blood, and accordingly the amount of atherosclerotic plaques in vessels, as well as helps to prevent adiposis and increases the sensitivity to insulin. According to opinion of scientists, betulin interacts with proteins, which bind SREBPs (sterol regulatory element-binding proteins) by transcription factors, which, as it is generally known, are important for activating expression of genes engaged in the biosynthesis of cholesterol, fat acids and triglycerides. Scientists confirmed by studies on cells that betulin lowered the activity of usually activated SREBPs genes, as well as the level of lipids. Comparative study was carried out on three groups of people, who were on a diet with high content of fats — on so-called “western diet”. For six weeks the first group got betulin, the second group – lovastatin, well-known statin, which lowers cholesterol, and the third group – placebo. In comparison with placebo, both preparations resulted in the decline of gaining weight, even if by different ways. Betulin compelled to burn more calories, while lovastatin rather diminished the amount of lipids digested from food. It was demonstrated in the study that betulin lowered the level of lipids in liver and adipose tissue to a greater extent than lovastatin. It also improved the sensitivity to insulin by affecting synthesis of fat acids and triglycerides.

ANTINEOPLASTIC ACTION OF BETULIN

Betulin can be effective in the complex therapy in the treatment of oncologic diseases. Under conditions of immunodeficiency, cancers appear more often. Even a simple injury reduces the immunity for a while. Tumor cells can grow even in conditions of oxygen deficiency, when normal cells cannot develop. The energy metabolism was reorganized in cancer cells with the result that they consume more nutritious substrates twenty times as much as normal cells. The cancer cell membrane is reorganized for enhanced admission of nutrients. Betulin fitting into the cancer cell cellular membrane blocks its reorganization on the initial stage and dooms it natural mortality (apoptosis). Hence, betulin acts selectively on sick cells and increases stability of healthy cells.

The antagonism effect of triterpenoids with alpha-tocopherol is of great importance to explain the mechanism of antitumoral

and antiviral action of betulin. It is known that alpha-tocopherol in prevailing amounts is localized in cancer cells providing to them higher antioxidant protection (effect of tocopherol oncotropy). If betulin molecules restore the structure of damaged biological membranes in normal cells under the "patch the holes" principle, then being in the membrane of a mutant cell, betulin prevents its further abnormal development and causes its natural mortality.

Treatment methods of oncologic diseases envisage the use of "hard" chemotherapy, which has a lot of prospects of success, but quite often it causes toxic and infectious complications. They can be structural damages of liver and kidneys, cardiac abnormalities, hemodepression etc. Imported correctors of cytostatic polychemotherapy are expensive and have undesirable effects. Betulin has multiple actions: hepatoprotective, antioxidant etc. and can be effectively used in the complex polychemotherapy as the adjuvant therapy.

INDICATIONS AND USAGE

Betulin can be prescribed as a powerful prophylactic preparation at the secondary immunodeficient states of any origin, at the "chronic fatigue" syndrome and especially for prevention of different viral diseases, in particular for prevention of the acute respiratory viral infection and flu. It can be used as hepatoprotective, choleretic, antilithogenous, antioxidative, anti-inflammatory, antitumoral, hypocholesterolemic, antiviral, immunomodulator, hypolipidemic, antihypoxant, gastroprotective, neuroprotective, antimutagene agent.

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Duly authorized signatory Natalya Yu. Gashkova