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BIOACTIVITY OF *MORUS ALBA* L. EXTRACTS – AN OVERVIEW

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ABSTRACT: Recently white mulberry has attracted a lot of interest as source of bioactive constituents used in phytopharmacy and in functional food formulation. In practice, active compounds are separated from plant material by extraction process using different solvents and extraction conditions. The most commonly solvents used for extraction are water, ethanol, methanol, acetone, ether and their mixtures. The extraction yield can be improved by the use of high temperature, high pressure, pulse electric field, sonication and microwave treatment. The effects of solvent concentration, solvent/plant material ratio, extraction temperature and extraction time are here discussed. This review intends to summarize and discuss the biological activities of mulberry extracts with regards to prevention and treatment of civilization diseases. The effect of phenolic compounds, flavonoids, anthocyanins, glycosides, terpenoides, enzyme inhibitors and other substances on human health are presented. The mechanisms of anticancer, anti-inflammatory, anti-obesity, anti-microbial, and antidiabetic effects are here discussed. It has also showed the protective effect of active compounds isolated from white mulberry on cardio-vascular and neurodegenerative diseases.

INTRODUCTION: Functional foods are foods with designed functional properties that prevents and reduces the severity of diseases. These diseases are common and global. The most common diseases include atherosclerosis, heart attack, high blood pressure, cancer, obesity, diabetes, osteoporosis, allergies and depression. Promotion of a healthy lifestyle and proper nutrition are identified as factors to prevent the development of these diseases. Quality of health functional foods are improved, mainly due to the presence in its composition of bioactive substances. These can include components such as polyphenolic compounds, fiber, probiotics and prebiotics, active proteins and peptides, polyunsaturated fatty acids, minerals and vitamins. Phenolic compounds including flavonoids are the highest group of natural antioxidants.

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Because of the common occurrence in the plant, they are a very important component of food. One of the known products containing bioactive ingredients is mulberry. The wealth of bioactive components contained in white mulberry, are increasingly used for the production of functional foods [1].

White mulberry cultivation has been associated with mulberry silkworm breeding for centuries. In China, the mulberry tree has been cultivated since 4 thousand years B.C., while it has been cultivated in Europe probably in the early Middle Ages. White mulberry (*Morus alba* L.), although widespread, is still underestimated. The plant is owned by *Moraceae*, a row *Urticales*, class dicotyledonous (Dicotyledones), clusters of angiosperms (Angiospermae).

It is monoecious or dioecious, with inconspicuous flowers odorless concentrated in small greenish inflorescences and small, edible fruit variable in color from white through red-pink to black. It occurs in the form of trees or tall shrubs. The natural environment of the white mulberry is Japan,

the Korean Peninsula, Central Asia, India and North-East Caucasus. Mulberry leaves were used mainly as food for silkworms, however, the known nutritional properties of white mulberry changed her destiny.

Both the leaves and the fruits can be found in many food products. Fresh white mulberry leaves for tea are processed by blanching and not blanching. In the first case tea color is green and the other black. Mulberry tea leaves have strong antioxidant properties [2]. In Korea, the mulberry leaves powder is one of the constituents of ice cream, giving them a pleasant taste while lowering blood glucose levels and thereby levelling their high sugar content. Thai researchers have developed a rice snack containing freeze-dried white mulberry leaves [3]. The leaves in the form of powder is mixed with rice, corn, soybeans, sugar, oil, vitamins and minerals, during the process of extrusion. Introduction to the rice "snack" 5% mulberry leaves powder gives this product strong antioxidant properties and increases in fiber. In India, Srivastava et al.[4] have developed a mixture consisting of lyophilized white mulberry leaves and wheat flour used for baking "paratha" - flatbread Indian popular throughout the Indian subcontinent and other Asian countries. Appendix mulberry leaves increases the overall protein content of the product and increases its durability.

Fresh squeezed juice from mulberry fruit contains significant amounts of antioxidants, including resveratrol, which is beneficial for a healthy heart. Mulberry fruit can also be used to produce jams, jellies, purees, sauces, juices, wine or food dyes. Dried mulberry fruit can be used as a sweetener for tea, or taken on long journeys, as food enhancers and regenerating power. White mulberry fruits, despite high nutritional value and a wide range of applications, however, are still difficult to access[5].

Extraction from mulberry leaves:

Plant materials contain only a small amount of active compounds therefore solid-liquid extraction is commonly used for recovery of these components. The extraction process is principal factor influencing biological activity of mulberry preparations used in medical and nutritional applications. The plant material used for extraction process can be fresh, fresh and homogenized, air-dried and grounded or powdered, and lyophilized and powdered. Material is usually macerated or suspended in solvent mixture at room or elevated temperature. The chemical composition of plant extracts is significantly influenced by the extraction parameters, as the type of solvent, the degree of fragmentation of the plant material, extraction time, temperature and pH of the extraction mixture **Table 1**.

In view to improve the extraction yield different techniques are proposed, as high temperature extraction, high pressure extraction, pulse electric field process, and extraction assisted by sonication or microwave [6]. At the choice of extraction method a thermal stability and nature of raw material should be taken into consideration. The selection of optimal conditions allows to maximize extraction yields and minimalize contamination with ballast substances. Thus, in order to separate as much as possible of the active substances from the mulberry without any loss of their activity.

Therefore, it is necessary to select the most optimal method of extraction and proper solvent compositions. Typical solvents for the isolation of biologically active substances are water, alcohol, acetone and ether. Water is used for extraction of highly polar components, such as carbohydrates, amino acids and glycosides. Ether and acetone are used for recovery of low polarity or aromatic compounds.

A solution of alcohol solvent - water, can be applied to a wide range of components of different inclination to solubility. After extraction mixture is filtered and solvents are exhausted by evaporation or vacuum evaporation.

Radojković et al.[7] have studied the effects of the concentration of solvent (40-80% ethanol), the extraction temperature (40-80°C), and the amount of solvent in relation to the material (10-30 ml/g) for the flavonoid extraction from mulberry leaves. The highest recoveries achieved by extraction of flavonoids was 53.44% ethanol, at 75.02°C, with 14.62 ml of solvent/g. Optimization of the extraction of flavonoids from mulberry leaves was also conducted by Ghasemzadeh and

Ghasemzadeh[8]. Researchers have studied the effects of solvent concentration (20-100%), the ratio of raw material to solvent (1:5-1:25), temperature (40-80ºC) and treatment time (1–3 h) for the extraction yield of flavonoids. The highest extraction efficiency was obtained with a concentration of 81.36% methanol, ratio raw material / solvent 1:15, at a temperature of 36.4°C, with a process for 2.37 h. According to Kim et al.[9] the best solvent was 60% methanol for extraction of polyphenols from mulberry leaves, and with compounds of high polarity. However, the most advantageous for the extraction routine proved to be extracted three times with 80 % ethanol, with a ratio of solvent to the amount of raw material to 30:1, at a temperature of 80°C for 3 h[10]. Adhyapak et al.[11] isolated rutin from dry mulberry leaves with 40% methyl alcohol, and the two extraction techniques: shaking for 60 minutes using ultrasound for 15 minutes. Researchers have found that extraction using ultrasound enhances the recovery routine. Extraction of flavonoids from mulberry leaves by microwave-assisted extraction (MAE) conducted Li et al.[12].

After the completion of the study it was concluded that the optimal parameters for extraction are extracted: 60% ethanol, with a ratio of feed/solvent 1:15, radiation power 560 W and the irradiation time of 5 minutes. MAE method made it possible to increase the efficiency of extraction of the soluble components contained in the leaves. Teng and Lee[13] defined optimal condition for microwave-assisted extraction to be 40% ethanol, irradiation time of 8 min, and microwave power of 210 W.

TABLE 1: EXTRACTION OF BIOACTIVE COMPOUNDS FROM WHITE MULBERRY

Plant material	Pretreatment	Solvents	Extraction parameters	Extracted substances	References
Leaves	Microwave dried, powdered	Ethanol	Temp. 100ºC, solvent evaporated at reduced pressure	Flavonoids	12
Leaves	Dried and powdered	Cold and hot water followed by 99.7% ethanol	Constant agitation 300 rpm 30 min.	Saponins, alkaloids, tannins, oxalate and flavonoids, trypsin inhibitors, phytate and phenolic compounds	14
Leaves	Air-dried	Water and methanol (15:85)	sonication, 25°C 1h	Mulberroside F	15
Leaves	Air-dried and powdered	Water	85-100°C, 1:50 w/v ratio, 85ºC, 1-3h	Raw extract	16,17
Leaves	Air-dried at 180ºC 7s., and powdered	75% methanol	1:6 w/v ratio, 45ºC for 4 h, solvent evaporation	Raw extract	18
Leaves	Air-dried, grounded	70% ethanol	1:15 w/v ratio, 30°C	Phenolics	1
Leaves, fruits	Air-dried	80% methanol/water	Ultrasonic –assisted for 10 min at room temp.,	Phenolic acids	19
Leaves	Dried and powdered	80% ethanol/water	1:15 w/v ratio, microwave-assisted 1 min with and 2 min without radiation, 5 min cycles, 560W	Flavonoids	12
Leaves	Oven-dried and powdered	80% ethanol/water	1:30 w/v ratio, temp. 80ºC. 5 times for 3h	Flavonoids	10
Leaves	Air-dried and grounded	68,3% ethanol/water. 53.4% ethanol/water.	1:29.19 w/v ratio, 68ºC. 1:14.6 w/v ratio, 75ºC.	Phenolics flavonoids	7
Leaves	Dried and pulverized	50% ethanol/water	1:5 w/v ratio, 80ºC for 1h	Phenolics	9

Stem bark	Dried and powdered	Acetone followed by ethanol	3 days acetone (1:2 w/v ratio) followed by 3 days ethanol (3:5 w/v ratio)	Phenols, terpenes	[20]
Root bark	Air-dried	70% ethanol/water	No data	antioxidants	[21]
Fruit	Homogenized	95% ethanol/0.1% HCl (1 ratio)	material:solvent ratio = 1:5(w/v), mixing, room temperature, 4h, dark	Anthocyanins	[22]
Fruits	Lyophilized	Methanol/1%HCl	1-2 day, 1:3 w/v ratio, filtration	Anthocyanins	[23,24]
Fruits	Dried at 70°C for 4 days, powdered	Ethanol	4:5 w/v ratio, 3 times, percolation technique, solvent evaporation	Raw extract	[25]
Fruits	Fresh	100% methanol	Room temperature, 24h, shaking	Morin	[26]
Fruits	Air-dried, grounded	Ethanol:water:acetic acid (70:29.5:0.5 v/v/v)	1:15 w/v ratio, 30ºC, 24 h, shaking	Flavonoids	[1]
Fruits	Fresh	80% acetone or 80% methanol	1:10 w/v ratio, 50ºC 30 min, shaking, solvent evaporation	Phenolics	[27]

Bioactive substances contained in white mulberry:

Mulberry belongs to the group of plants of pharmacological importance, and includes various morphological parts of bioactive compounds. These are mostly polyphenolic substances, flavonoids, anthocyanins, lectins, oligosaccharides, enzymes, digestive enzyme inhibitors, stilbene glycosides, anti-bacterial substances, unsaturated fatty acids and many other physiologically active substances. These ingredients are present in the leaves, fruits, roots and stems, however the richest source of bioactive substances are in the leaves[28].

Srivastava et al.[4] marked the basic composition of mulberry leaves, and showed that the leaves protein content is between 15-30%, fat 2-7.9%, fiber 9.9-13.8%, ash and carbohydrates 13-17% 9.7-39.7% . White mulberry leaves are also rich in minerals like iron, zinc, calcium, phosphorus and magnesium. Particularly noteworthy is the content of calcium 786-2726 mg/100 g dry matter, phosphorus 970 mg/100 g dry matter and magnesium 720 mg/100 g dry matter. Among the vitamins included in the white mulberry were labeled ascorbic acid and β-carotene.

The content of ascorbic acid is 100-200 mg/100 g dry matter, and its operation is extremely important due to the purification of the body's cells from free radicals. The presence of essential unsaturated fatty acids was also identified in the white mulberry fruits. Among the most monounsaturated fatty acid there is the highest amount of palmitic acid (22.4%) and oleic (10.5%) and is the highest amount the polyunsaturated linoleic acid (57.26%) [4].

Polyphenols: In terms of the medinal value of white mulberry, the most important role is played by polyphenols. Chu et al [29] identified in each of the five parts of the morphological parts white mulberry (leaves, fruits, roots, bark and stem) routine (flawonol derivative), umbelliferon (coumarin derivative), chlorogenic acid (phenolic acid), kaempferol (flavonol) apigenin (flavone), luteolin (flavone), quercetin (flavonol), morin (flawonol derivative), caffeic acid (phenolic acid) and gallic acid (phenolic acid). It was found that the highest amount of routine occurs in fruits and leaves (293.5 mg/g and 179.1 mg/g), of umbelliferone - in roots and bark (538.7 mg/g, 289.6 mg/g), chlorogenic acid and kaempferol- in fruit (226.9 mg/g, 5.8 mg/g), apigenin - in the stem and leaves (43.8 mg/g, 42.7 mg/g), luteolin- in the root (4.3 mg/g), quercetin - in fruits (15.2 mg/g), morin - in bark (17.2 mg/g), caffeic acid- in fruits (17.2 mg/g) and gallic acid – in roots (14.7 mg/g).

Many valuable data on chemical composition of mulberry were published by Lin and Lay [28]. Distribution of particular bioactive substance in different morphological parts of mulberry is shown in **Table 2**.

TABLE 2: BIOACTIVE SUBSTANCES OCCURRING IN WHITE MULBERRY

Anatomical part	Substances	Active compounds	Ref.
Leaves	Phenolic compounds	Apigenin, quercetin, morin, luteolin, gallic acid, caffeic acid, chlorogenic acid, syringic acid, coumaric acid, ferulic acid, rutin, umbelliferone, astragalin, magniferin, sanggenon J and K, morusin, cyclomorusin, atalantoflavone, kaempferol	1, 19, 29, 30, 31, 32, 60
	Fatty acids	palmitic acid, oleic acid, linoleic acid, eicosanoids	19
	Enzyme inhibitors	Moranoline, 1-deoxynojirinmycin	33
	Lectins	MLL 1 i MLL 2 (sialic acid binding) hemagglutinin, phytoagglutinin, phytohemagglutinin and phytosins	33, 34
Stem bark	Phenolic compounds	Maklurein, rutin, isoquercetin, resveratrol, morin, apigenin,	28, 29, 35
	Triterpenoids	moruslupenoic acid A, moruslupenoic acid B, moruslanosteryl acetate	36
Root bark	Phenolic compounds	Luteolin gallic acid, sinapic acid, resveratrol	19, 29
	Mulberry flavonoids	Sanggenols, kwanon, mulberrofuran	32
	Glucosides	Moran, 1-deoxynojirinmycyna, glucoside, cyanidin 3-*O*-β-D-glucopyranoside, moracin,	15, 37
	Lectins	albanol	38
	Enzyme inhibitors	oxyresveratrol	30
Fruits	Phenolic compounds	Protocatechuic acid, protocatechuic aldehyde, apigenin, luteolin, quercetin, morin, caffeic acid, gallic acid, chlorogenic acid, hydroxybenzoic acid, p-coumaric acid, ferulic acid, kaempferol, rutin, umbelliferone	2, 19, 27, 30, 35
	Fatty acids	Palmitic acid, oleic acid, linoleic acid	35
	Glucosides	Rutinoside cyanine, cyanine glucoside	22

Enzyme inhibitors:

Flavonoids contained in the leaves of the white mulberry were proved to be inhibitors of aromatase, an enzyme catalyzing the hydroxylation reaction, leading to the formation of estrogens (estradiol and estrone) from androgens (testosterone and androstenedione). This enzyme is also used in the hormonal treatment of breast cancer in women undergoing menopause. Flavonoids bind to the active site of aromatase in the orientation in which rings A and C "mime" the rings D and C of androgens. Among the natural flavonoids inhibitin aromatase activity are: mulberroside F, routine, astragalin (3-glucoside, kaempferol) [39].

Lee et al. [15] examined the dried leaves of the white mulberry to see if bioactive components in them inhibit the biosynthesis of melanin. They showed that glucopyranoside moracin - mulberroside F (moracin M-6, 39-di-Ob-D-glucopyranoside) inhibits the activity of tyrosinase, the enzyme catalyzing the first step in the synthesis of melanin, and thus prevents the formation of melanin. Mullberroside F (moracin M-6, 39-di-O-β-D-glucopyranoside) also inhibits the conversion of DOPA to DOPA-chrome in the process of melanogenesis. Due to the high potential antioxidant it eliminates free radicals, helping to protect against autoxidation. Tyrosinase is also known as polyphenol oxidase (PO). In addition to bioactive components that inhibit tyrosinase, white mulberry leaves also isolated the components α-glucosidase inhibitors, including prenylated Stilbenes, the new α-glycosidase inhibitors, such as chalcomoracin, moracin C, D and moracin N [40]. White mulberry leaves also exhibit inhibitory activity against α-glycosidase, and therefore consumption of the mulberry leaves tea can help in antidiabetic action. Potent inhibitor of α-glucosidases is commonly known DNJ (1-deoxynojirimycin). Kim et al. [37] have developed a reliable way of marking in DNJ in white mulberry leaves. From 0.1 g of lyophilized leaves DNJ was extracted twice with 10 ml of 0.05 M HCl aqueous solution and then centrifuged for 15 s and derivatized with 9-fluorenylmethyl chloroformate (FMOC-Cl).

This allowed 99% recovery from DNJ leaves. There was also a connection between the content and the activity of DNJ α-glycosidases. It was found that with increasing DNJ (in mg / ml), inhibition of the enzyme activity increased.

Hansawasdi and Kawabata [41] examined the impact of time of infusion the white mulberry leaves content of α-glycosidase inhibitors, and maltase sucrose on a dry weight basis. After testing, it was observed that after 3-5 minutes of infusion of 1 g of white mulberry leaves in 100 ml of hot water (98°C), they showed inhibitory activity. A decrease of glucose levels in serum by inhibiting the absorption of carbohydrates from the intestine was also confirmed.

The white mulberry leaves also include compounds responsible for the inhibition of acetylcholinesterase (AchEIs), which are elements important to the treatment of Alzheimer's disease. Priya [35] has demonstrated that three flavonoids contained in white mulberry leaves, myricetin, kaempferol and luteolin, exhibit high activity for the inhibition of acetylcholinesterase and therefore showed high potential of white mulberry, allowing its use in the treatment of Alzheimer's disease.

Medical properties of white mulberry extracts:

Bioactive substances present in the white mulberry are known to inhibit the proliferation of tumor cells, of characteristics of antidiabetic and anti-inflammatory; to protect against neuronal degeneration, aging skin and reduce the risk of diseases of the cardiovascular system [35]. Most of active compounds are in leaves, but many of them can be found in the bark of branches and roots, and in fruits. Mulberry is used in traditional medicine of India, China, Russia and Peru as a medicinal plant for hundreds of years, and modern science brings more and more data about its bioactive components and mechanisms of their effects on human and animal body.

Anticancer activities:

Mulberry is a known source of compounds which inhibit the initiation and development of cancer. Their mechanism of action is omni-directional and consists in the elimination of the reactive form of oxygen and nitrogen, and which reduces the number of negative mutations, reducing inflammation, promoting apoptosis and the activation of the immune system.

Foreground protective functions primarily serve a number of antioxidants present in the mulberry tree. These include flavonoids and polyphenolic compounds, including (+)-catechin, procyanidin B1, cinnamic acid, apigenin, quercetin, isoquercetin, morin, luteolin, chlorogenic acid, kaempferol, umeliferon, rutin, gallic acid, resveratrol, maklurine, terpenoids, and many others. Extracts of white mulberry leaves are particularly rich in chlorogenic acid, siringic aldehyde and vanillic acid [19].

Methanolic and acetonic, sugar-free extracts of fruits of *Morus alba* and *Morus nigra* exhibit antioxidant potential determined by ABTS at the level of 0.75-0.78 mmol Trolox/g and the total content of phenolic compounds is 104-213 mg/g [27, 42]. The high antioxidant potential of mulberry extracts is also confirmed by the results of an FRAP and DPPH methods. In this case black mulberry (*M. nigra*) stands out in particular.

Based on *in vitro* and *in vivo* studies have demonstrated that many of the phenolic compounds contained in the mulberry tree have anticarcinogenic activity. Most of the tests were performed on cellular models using various human cell lines. A key role in normal processes of apoptosis play transcription factors initiating apoptosis in cells with damaged DNA. The best known factors of this type include the p53 protein encoded by the p53 gene. Among the bioactive substances present in the white mulberry are anthocyanins. Chinese researchers have demonstrated that anthocyanins from mulberry show the activity against gastric cancer through the mechanism of induction of apoptosis via the activation of pathways p38/jun/Fas/FasL and p38/p53/Bax that started cell death [23].

In the presence of mulberry's anthocyanins, the inhibition of lung cancer was observed. Chen et al. [24] have found that 3-rutinoside of cyanidin and 3-glucoside of cyanidin inhibited migration and invasiveness of A549 cells of lung cancer. The presence of both compounds reduced the expression of matrix metalloproteinase-2 (MMP-2) and of plasminogen-dependent activator of urokinase, and in addition, these compounds increased the expression of inhibitors of both these proteins. At the same time both anthocyanins

weakened the activation of the transcription factor c-Jun and regulator of DNA transcription NF-kB. Antimetastatic (antimetastatic) effects on murine B16 melanoma cells showed resveratrol isolated from the methanolic extract of white mulberry.

Flavonoids also have an anti-cancer effect . Dat et al. [32] have isolated 11 flavonoids from the leaves of the white mulberry. These researchers have showed that the isolated compounds were characterized by the cytotoxic activity against HeLa cells, breast cancer (MCF-7) and liver cancer (Hep3B). The strongest activity showed murysyna, sanggenol L, M, and different types of furans (mulberryfurans). Among the active compounds contained in mulberry leaves are mentioned lectin [43]. These are proteins or glycoproteins binding with carbohydrates

The best-known lectins are hemagglutinins, phytoagglutinins, phytohemagglutinin and phytosins. In the plant's world the most widely described lectin is concanavalin A. Lectins play an important role in cell adhesion and the role of structure-information, that is found on the cell surface as a specific marker recognized by the immune system. The biological activity of the plant lectins is determined mainly by the properties of their immunomodulatory and anti-proliferative, which is used among other things in cancer therapy. In the absence of a set of lectins or excess, modified cell is recognized as an antigen and determined as a target for destruction by immune cells. If in that way, damaged cells are eliminated, then the lectins play a supportive role in apoptosis, but in this way the normal cells can be destroyed. In recent years, attempts were made to intentionally place plant lectins in the form of a drug on the surface of tumor cells and the destruction of malignant tumors.

Antiproliferative lectin (MLL) was detected in the mulberry with a molecular weight of about 56 kDa [33]. The purified protein showed agglutination ability at 40°C. Lectin showed antiproliferative capacity against breast cancer cells (MCF-7) and colon cancer (HCT-15). Demonstrated that MLL induces significant morphological changes and DNA fragmentation combined with apoptosis of both type of tumor cells. The cytometric analysis showed increased production of caspase 3 and stop the growth of the cells in the G0-G1 phase.

Apoptotic activity against cancer cells also demonstrated albanol A (syn. mulberryfuran G). This substance has been isolated and extracted from the root bark of white mulberry. Kikuchi et al. [38] have showed, that the substance is cytotoxic and induces apoptosis in leukemia cells (HL60). In addition, the substance inhibited the activity of human DNA topoisomerase (TOPO) I and II. It shows at the same potent cytotoxicity, the interaction of albanol with tumor cells is accomplished by receptor stimulation of cell death (death receptor target), and on the pathway of mitochondria through inhibiting Topo II. Currently albanol A is considered as a potential treatment for leukemia.

Inhibition of diabetes:

Diabetes is a chronic metabolic disorder involving the partial or total deficit of insulin, that leads to hyperglycemia and disturbances in the metabolism of carbohydrates, fats and proteins. Chronic hyperglycemia leads to multiple organ failure. The most common form of the disease is type 2 diabetes, which consists of a reduced sensitivity of tissues on insulin.

In traditional Asian medicine, the white mulberry is mentioned. Most of the publications on antydiabetic activity of extracts of mulberry describes experiments using experimental animals, particularly rats. The diabetes in these animals was induced by supply of streptozotocin or alloxanu. Natural plant growth regulators, such as indole-3-acetic acid and its natural and synthetic analogues, such as indole-3-butyric acid, indole-3-propionic acid, L-tryptophan, and p-chlorophenoxyacetic acid inhibit the activity of insulinase in vitro, and are hypoglicemic in normal rats.

It is estimated that the antidiabetic activity has around 200 chemical compounds. Studies of diabetes of rats has shown that the consumption of 600 mg/kg/day of the fraction rich in flavonoids from root bark of mulberry reduces blood glucose levels due to increased insulin levels and a reduction of lipid peroxides [21]. The consumption of 0.5-1 g/kg of mulberry leaves lowers blood glucose

levels and lower blood pressure of ill rats. Consumption of mulberry leaf extract reduces lipid peroxidation, increases the activity of hexokinase, glucose-6-phosphate dehydrogenase and lactate, and inhibits the activity of glutathione transferase - glucose-6-phosphatase [16]. Experiments conducted on rabbits have shown that consumption of the ether extract from the leaves in an amount of 200 mg/kg caused a marked decrease in the level of glucose [44]. Similar results were obtained in studies in mice [45]. The experiments suggest that the activity of extracts of white mulberry rely primarily on their antioxidant activity.

In maintaining of proper blood glucose level are useful inhibitors of intestinal alpha-glucosidase and maltase. An example of such an inhibitor is moranoline and alkaloid inhibitor 1-deoxynojirimycin (DNJ), especially great interest aroused the latter. It is considered as the strongest natural inhibitor of alpha-glucosidase.

There is ample evidence that, for the efficient operation of extracts of mulberry leaf required a long residence time of the active ingredients of mulberry in the body. This can be achieved by frequent administration of the extract, which was confirmed in studies on human volunteers. It should also be noted that inhibition of alpha-glucanases and extracts of mulberry stimulate insulin secretion (fagomyns) and lower cholesterol (phytosterols). Extracts of white mulberry reduce the number of adverse side effects resulting from the development of diabetes, such as cataracts and abnormalities in the functioning of neurotransmitters [17].

Prevention of obesity:

Obesity is linked with metabolic syndrome that results in the disturbance in the metabolism of carbohydrates and fats. The syndrome is accompanied by a lot of metabolic diseases such as diabetes, hypercholesterolemia, and hyperlipidemia. Obesity is a complex process and regulated by many factors. The most important ones include the amount of food that is consumed, the scope of his digestion, nutrient absorption from the gastrointestinal tract, and finally the growth rate of body fat determined by the efficiency of the process of adipogenesis and lipid synthesis.

Literature data indicate that ingestion of preparations obtained from mulberry has influence on all of the factors contributing on the metabolic syndrome. Consumption of fruits of mulberry or its extracts containing inhibitors of digestive enzymes, mainly alpha-glucosidase, decreases the supply of glucose and, consequently, lower blood glucose levels. The lower dose of glucose, results in less weight gain, and thus prevents obesity. This effect was confirmed by studies in mice and rats with induced obesity, which showed that chronic administration of alcoholic extracts of mulberry leaves exerts anti-obesity [46].

A big reduction in blood glucose, insulin and triglyceride levels in the blood were obtained after supply to mice of the aqueous extract from a mixture of Korean red ginseng, leaf of banaba and mulberry (1:1:1). At the same time an increase of expression was observed of the hepatic PPAR-α mRNA, adiposic (adipose tissue) PPAR-γ mRNA and liver LPL mRNA. This implies a significant increase of sensitivity of animals on insulin by regulating PPAR-mediated lipid metabolism, after administrating a diet enriched in extracts of these three plants [47].

Mulberries also contain lipase inhibitors and factors governing the process of lipolysis, which affects the formation of obesity. Kim et al. 2010 [48] showed that extracts from mulberry *Morus bombycis* inhibit the action of lipases, while increasing the lipolysis in adipocytes, leading to a reduction in the level of intracellular triglycerides. A supply of db / db to mice powdered mulberry leaves together with pioglitazone inhibited weight gain, reduced lipid peroxidation and decreased triglyceride levels [45].
An anti-obesity effect of 1-deoxynojirimycin from mulberry was determined by Tsuduki et al. [49].

Cardiovascular disease:

Diseases of the cardiovascular system are among the diseases of civilization, and are one of the main causes of death. The main cause of them is considered poor nutrition, hypertension, low physical activity, high cholesterol, excessive alcohol consumption and metabolic syndrome that are associated with obesity and stress. Traditional medicine recommends the use of mulberry water infusions to treat high blood pressure, reduce

cholesterol and protect against atherosclerosis [35]. Butanol and water extracts of root bark mulberry have an anti-convulsive activity and anti-hypertensive in mice, rats, guinea pigs and dogs [50]. The butanol extracts from mulberry leaves lower serum cholesterol and prevent atherosclerosis [51].

It is also known that there is a strong influence of ethyl acetate extracts from the leaves of *Morus alba* on the blood vessels. Thanks to content of the routine, apigenin, and quercetin extract, we have the effect of relaxation. It is the result of blockade of calcium receptors and voltage-dependent calcium channels (voltage-gated calcium channels), which reduces the flow of Ca^{2+} ions into smooth muscle cells of blood vessels.
Mulberry leaf extracts have also shown an antiatherosclerotic effect. Studies in mice have shown that administration of the mulberry extract in an amount of 1% of the diet reduced by 40% atherosclerotic lesions in the aorta. Extracts of the mulberry leaf inhibit the oxidative modification of low density lipoprotein (LDL), which is the primary cause of atherosclerosis lesions [18].

Inhibition of neurological diseases:
One of the most severe neurodegenerative diseases is Alzheimer's disease consisting the progressive mental dullness. It affects mainly elderly people over 65 years old. So far, full genesis of this disease is not known, but a key role in its development is attributed on oxidative stress. This is observed on lipid peroxidation, reducing the degree of saturation of fatty acids, increasing the concentration of iron and aluminum and markers of oxidative DNA damage. Many laboratory studies demonstrated the protective role of extracts of white mulberry against Alzheimer's disease. These extracts contain oxyresweratrol, a natural hydroxystilbene and at the same time acts as an inhibitor of tyrosinase. This enzyme catalyzes the ortohydroxylation of tyrosine to DOPA and further converted into dopaquinone. Oxyresweratrol demonstrated neuroprotective activity in cortical neuronal cells (culture cortical neurons), in SH-SY5Y cells as well as in models of in vitro and in vivo [30]. It has showed that the methanol extract of mulberry leaves exerts anti-dopaminergic effect by blocking D2 receptors. Oxyresveratrol has a neuroprotective effect against Alzheimer's disease and stroke.

Alzheimer's and Parkinson's are combined with the exhaustion in the brain γ-aminobutyric acid (GABA). The acid acts as a neurotransmitter in the central nervous system. Disturbances in its level results in the development of many neurodegenerative diseases. Kang et al. [52] pointed out the possibility of the brain protection against adverse changes by introducing a source of GABA to your diet. The authors showed that the administration of an extract containing GABA is neuroprotective on PC12 cells, protecting from hydroxyl radicals, and delays the ischemic stroke disease, (cerebral ischeia).

Among the causes of acute and chronic neurological disorders it mentions also the excessive glutamate receptors activation, so-called. excitotoxicity. Stimulation of these receptors provokes a massive influx of calcium ions and mitochondrial membrane potential change and, consequently, increased production of reactive oxygen species (ROS). Both processes occur before initiating the process of apoptosis and neurodegenerative diseases. Compos-Esparza et al. [53] have shown that the processes can be prevented by giving mangiferin and morin, phenolic components of extracts of white mulberry. The authors explained the molecular mechanism for this phenomenon.

One of the diseases associated with vascular diseases is vascular dementia. This is the second dementing disease in the world after Alzheimer's disease. It is caused by the slower blood flow to the brain due to constriction of blood vessels. In this case it plays a central role in the oxidative stress and the cholinergic system. This disease is common in older people, particularly those after stroke. In practice, the treatment of these changes are difficult and expensive.

In recent years, attention was paid to the protective effect of extracts of mulberry. This applies particularly to alcoholic extracts, administered in the form of wine made with mulberry fruits. In rats treated with the ethanol extract from fruits of white mulberry, results of an improvement in memory

test performance in the water maze and decreased activity of acetyl-cholinosterase and an increase in the density of neurons in the hippocampus was observed [25, 54, 55]. The results clearly showed neuroprotective activity of extracts of mulberry fruits. Additionally, it was observed that the administration of mulberry fruits relieves brain cell damage and slows the weakening of memory. Extracts of the mulberry leaf were also used to relieve headaches, depression, schizophrenia and its action was comparable with the action of the drug clozapine [56].

Liver protection:

The liver is the main organ regulating the homeostasis of the body. In the liver, a number of biochemical pathways of metabolism of nutrients are carried out, and here changes related to the protection of the organism against toxins are placed. In traditional medicine, a number of herbs were used to restore normal liver function after ingestion of toxic substances. One such plant is the white mulberry. Hogade et al [57] demonstrated that administration of the extract to rats with carbon tetrachloride-induced tetrachloride (CCl4) hepatotoxicity has a protective effect on the liver. These authors used the ether extracts (petroleum ether), chloroform, alcoholic and aqueous.

In alcoholic extracts were present alkaloids, flavonoids, carbohydrates, tannins and steroids, and in the aqueous extract were determined carbohydrates, flavonoids and alkaloids. The application to animals aqueous and alcoholic extracts revealed the protective effect by lowering the level of biochemical markers for hepatitis and reduce damage of hematocytes [57]. Similar studies conducted by Kalantari et al. [58]. They showed a protective effect of alcoholic extract of white mulberry leaves at a dose of 800 mg/kg. After administration of the extract, significantly lowered levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels and reduced histopathological changes was observed in the liver.

Antimicrobial activity:

In the last two decades, research was conducted to search for new substances with antimicrobial activity, which is associated with more and less effective of antibiotics that are produced. Attention is also to the source of plant. In traditional medicine, white mulberry, next to the medicinal properties, is known for its antimicrobial properties [59]. Among the substances present in the white mulberry leaf extracts with antimicrobial effects is present of saponins, tannins, alkaloids and flavonoids. Paiva et al. [60] indicate that the flavonoids from *Morus alba* inhibit *E. coli*, *Salmonella* Typhimurium, *Staphylococcus epidermis*, *S. aureus*, *Candida albicans* and *Saccharomyces cerevisiae*.

In studies on the antimicrobial properties of white mulberry extract the soluble proteins were also used. Among antimicrobial ingredients of white mulberry are mentioned a p-cresol, phenol and morin. Manjula and Shubha [61] have shown that thermostable proteins from *M. album* showed growth inhibitory activity of *Escherichia coli*, *Pseudomonas aeruginosa, Bacillus subtilis* and *Staphylococcus aureus*. Ayoola et al. [14] studied the antibacterial activity of ethanol extracts of *M. alba* from leaves. They showed that the ethanol extract inhibits the growth of Gram-negative bacteria *Escherichia coli, Pseudomonas aeruginosa*, *Neisseria gonorrheae* and gram-positive bacteria *Proteus vulgaris, Staphylococcus aureus* and *Streptococcus faecium*, and fungi *Aspergillus tamari, Aspergillus niger, Fusarium oxysporum* and *Penicillium oxalicum*.

The value of minimum inhibitory concentration MIC of the extracts obtained by means of hot water for these bacteria were in the range 450-600 mg / ml, and ethanol extracts of 800-1100 mg / ml. The MIC for fungi was much lower and amounted to 55-70 mg / ml and 70-85 mg / ml Modi et al. [62]. Among microorganisms inhibited by extracts of white mulberry also lists *Streptococcus mutans* causing dental caries (dental aries), recognizing the value of MIC for the bacteria to be 8 mg / ml.

In the scientific literature, you can find the information on the antiviral activity of extracts of white mulberry.

CONCLUSION: The data show clearly that the white mulberry is a rich source of bioactive substances that protect the human body against

diseases of civilization. Its action is versatile, and bioactive substances are arranged in different parts of the plant. Protective effects of phytochemicals in white mulberry is mainly due to a high content of phenolic compounds and high antioxidant capacity of the plant. Especially rich in these substances are leaves of mulberry.

It should also be noted a large amount of data explaining the mechanisms of the therapeutic effect of mulberry components based on model studies and clinical trials. The growing interest in natural pharmacological agents used for the prevention and treatment of lifestyle diseases should lead to greater use of white mulberry. The results justify the desirability of research to obtain new varieties of this plant which are rich in active phytochemicals, and to develop effective methods for the separation of bioactive substances.

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