Chapter

Phytotherapy and Liver Disease

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Abstract

Hepatoprotective agents are medicines or dietary supplements that are used as an adjunct to the treatment of acute and chronic viral hepatitis, liver cirrhosis, hepatocellular carcinoma prevention, as well as other liver diseases. Experiments on animals and cell cultures have shown that natural compounds can alleviate and prevent pathological changes in the liver. In the past few years, considerable attention has been paid to medicinal herbs with hepatoprotective, antioxidant, and immune properties. The plants contain numerous phytochemicals, including polyphenols, phenolic acids, coumarins, styles, tannins, lignans, and lignins. These compounds include silymarin, curcumin, picroside, kutkoside, phyllanthin, hypophyllanthin, glycyrrhizin, glycyrrhizin, berberine, luteolin, quercetin, coumarin derivatives (4-methylumbelliferone), and others. Many studies have been aimed at collecting data on some types of edible plants and fruits (grapefruit, cranberries, grapes, beets, cacti, chamomile, spirulina, propolis) that have shown hepatoprotective effects.

Keywords: plants, phytochemicals, dietary supplements, hepatitis, liver cirrhosis

1. Introduction

In liver disease treatment besides causal medicines, there are also antihepatotoxic, hepatotropic, and hepatoprotective agents. Hepatoprotective medicines or dietary supplements are used as an additional treatment for toxic liver damages, acute and chronic viral hepatitis, cirrhosis, and other liver diseases. There are numerous plants and traditional formulas used in liver disease treatments around the world.

2. Hepatoprotective plants and phytochemicals

Hepatoprotective chemicals are found in large number of medicinal herbs, out of which several were proven as very effective in various liver damages. Those compounds include silymarin, curcumin, picrorhiza and kutkoside, phyllanthin and hypophyllanthin, glycyrrhizin, berberine, luteolin, quercetin, and others [1]. Plants with polyphenol content (green tea) also indicate effectiveness in liver protection. It is determined that these compounds protect liver cells from various toxins, ischemic injuries, radioactive radiation, iron intoxication, and hepatotropic viruses [2]. The research suggests that these compounds increase protein synthesis, reduce tumor promoter's activity, stabilize mastocytes, modulate immune system, and have anti-inflammatory and anti-fibrotic effect. Many researches aimed at gathering information about some species of plants and fruits (grapefruit, cranberry, grapes, cacti, chamomile, and spirulina) which are often consumed and which have already shown hepatoprotective effects [3].

2.1 *Aloe vera* (lat. *Aloe barbadensis* M)

Aloe vera was named after botanist Miller who discovered and registered it in the registry of medicinal herbs. In the nature, it grows only in warm and dry climate areas, such as the Caribbean and Mexico. It has saber-like, pointy leaves which in its form remind of a rose and grow close to the ground. There are more than 250 species in the world, and only four have healing effect, among which predominantly is *Aloe vera* Barbadensis M. It was used as a medicine 6000 years ago in ancient Egypt, and back then it was known as "the herb of immortality." The most frequently used part of the plant is its gel, jelly-like mass from the inside of the leaf. *Aloe vera* has nutritious effect on every cell of the human organism, and because of its nutritional value and exceptional healing abilities, it is often called as "the queen of medicinal herbs." The gel contains more than 240 nutritious and healing ingredients: Vitamins A, B1, B2, B3, B6, B9, B12, C, and E, more than 20 minerals (magnesium, manganese, zinc, copper, chrome, calcium, potassium, iron), and 20 types of amino acids. Aloe extract called aloe emodin, in vials, can block the growth of cancer cells on the head and neck. Acemannan from the leaf can incite immune cells in mice to fight against cancer. In vials, di (2-ethylhexyl) phthalate (DEHP) stops the development of leukemia cells. Two studies from 2010 showed positive effect in mouse skin cancer treatment. However, in one study, some Aloe products indicated the increase of skin cancer cells. Research in Italy tested the effect of *Aloe vera* on chemotherapy treatment of persons with lung, intestine, and stomach cancer. The cancer was under control or reduced by 67% in patients who received both aloe and chemotherapy treatment, whereas by 50% with patients who only received chemotherapy. Patients using *Aloe vera* had better life quality and less side effects of chemotherapy [4–7]. Even though *Aloe vera* is generally considered as hepatoprotective [8, 9], there are also some cases described in literature where liver damage was caused by *Aloe vera* [10].

2.2 Artichoke (*Cynara scolymus*)

Artichoke is a highly appreciated plant in modern phytotherapy. The healing properties are found only in leaf but not in the flower. The most important active substances of artichoke are caffeine acid and its esters (cynarine); the concentration of which is significantly reduced in the process of drying. The other ingredients include chlorogenic acid, sesquiterpene lactones, and flavonoids. It has choleretic, antioxidative, and hepatoprotective effects. It reduces cholesterol levels in blood; it is used in dyspepsia, lack of appetite, and irritated colon; it helps in prevention of formation of cholesterol-based gallstones, and it is used in drainage treatment. Artichoke is a fairly safe plant. However, it occasionally may cause an allergic reaction. Contraindications in artichoke use include obstruction of bile ducts and artichoke allergy [11].

2.3 Cranberry (*Vaccinium macrocarpon*)

There are available data that cranberry as medicine was used as far back as among American Indians (Native American medicine). It is a bush plant with red berries originating from North America. Concentrated cranberry is called brusnicin. The most healing agent from cranberry is arbutine which acts both as antibiotic and diuretic, and it can be found in leaves. Cranberry contains hippuric acid with powerful antibacterial effect, and thus it is used in prevention or treatment of various infections (helicobacter pylori and candida). It is also recommended in treatment of urinary tract infections caused by *E. coli* [12]. Berries are rich in vitamins B and C, iron, copper, and manganese. It is highly a potent combination that strengthens weakened immune system. Berries are full of nutritious fibers that improve

digestion, metabolism, and liver function. It is rich in antioxidants that reduce the harmful effect of bad blood cholesterol. It contributes to protection from free radicals and protects cardiovascular system [13]. Cranberry contains anthocyanins and proanthocyanidin which may improve eye sight and reduce blood sugar level [14]. It is a profound laxative, helps digestion, and was also very useful in prevention and treatment of gonorrhea, arthritis, rheumatism, diarrhea, skin and eye infections, sex organs, liver, cold, gallstones, prostate cancer, and urinary tract. It slows aging process and reduces underlying problems such as loss of memory and coordination. According to Canadian Journal of Microbiology, increasing concentrations of this extract reduce the bacteria's production of urease, an enzyme that contributes to the virulence of infections. Professor Nathalie Tufenkji from McGill University in Montreal states: "While the effects of cranberry in living organisms remain subject to further study, our findings highlight the role that cranberry consumption might play in the prevention of chronic infections" [15].

2.4 Beetroot (*Beta vulgaris*)

Ancient Romans were familiar with and used beetroot as food, not only its roots but its leaves as well. Although they had no idea about real reasons for its healing ability, even Dioskurides and Galen highly appreciated this vegetable and attributed great healing abilities to it. Only with the development of biochemistry it was possible to demonstrate what are the most valuable ingredients in beetroot and it is possible to confirm 2000-year-old assessment by ancient physicians. Back in 1957, researches came up with unquestionable evidence about anticancerogenic features of a beetroot. It is rich in minerals: the highest amount is potassium, then sodium, phosphorus and calcium, iron, magnesium, fluorine, also copper, sulfur, iodine, and bromine, and there are also in traces rare and valuable elements such as rubidium, cesium, and strontium. Beet's root and leaves contain apple, wine, and lemon acids. Beet also contains significant amount of cobalt used for creation of vitamin B12, B1, B2, C, and P. Amino acids (asparagine, glutamine, and betanin) are found in beetroot juice and have beneficial effect on brain and nerve activity. Betanin strengthens blood vessels, regulates blood pressure (especially in low blood pressure), reduces blood cholesterol, improves substance exchange (improves urine excretion, uric acids, and salts), as well as liver function. It increases bile excretion, and thus it is also recommended to people who have liver and bile duct diseases. It has calming effect on a nervous system; it is suitable for adrenal glands treatment; it has positive effect on stomach and intestine function, and thus it regulates feces excretion as well. This vegetable is ideal for physical and psychological strengthening of exhausted people thanks to glutamine and aspartic acids which are very important for proper brain and neural function [16, 17].

2.5 Grapefruit (*Citrus paradisi*)

Grapefruit is an evergreen tree growing up to 6 meters in height. It requires warm climate and big humidity. Fruits can grow up to 15 cm and can have yellow or orange colored peel. It is rich in vitamins C, B, P, and phytochemicals. Grapefruit strengthens immunity, regulates metabolism, and prevents cancer development, especially in lungs and colon [18]. It is abundant in minerals, magnesium, and potassium as well as organic acids, ethereal oils, sugars, microelements, pectins, and pigments. It has refreshing effect on human organism. Grapefruit also helps with atherosclerosis. Grapefruit juice has exceptional antibacterial, antifungal, and antiviral capabilities [19]. In Japan, experiments on mice showed that tumor growth stopped after mice were being injected under the skin with grapefruit extract. One grape a day is proven

to reduce the risk of pancreatic cancer by half [20]. It reduces blood cholesterol levels. However, some substances found in grapefruit can have some interactions with metabolism of some drugs, if taken simultaneously, thus increasing the concentration of these drugs in blood and provoking serious, even life-threatening reactions. It is mostly connected to drugs used in treatment of cancer, depression, anxiety, angina, high blood pressure, high level of lipid cholesterol, HIV infection, different infections, and heart arrhythmias. There is evidence that even the smallest glass of grapefruit juice can cause unwanted and dangerously increased level of drugs in blood, and these effects can last for more than 3 days [21, 22].

2.6 Spirulina

Spirulina is blue-green, fresh water algae which grows in lakes and fish ponds around the world. Being 3.6-billion-year-old, it is one of the oldest residents of the planet Earth. People of Africa, North America, and Asia are using it for thousands of years. Old Aztecs consumed it in the form of dried biscuits. According to some scientists, it could solve world hunger issue since it is full of proteins, minerals, and other nutritious substances. Due to significant amount of vitamin B12, it helps in development of healthy nerve tissue and in metabolism of every cell, including those of the liver. Mineral content consists of potassium, calcium, magnesium, iron, sodium, phosphorus, zinc, and selenium. Rich in chlorophyll, it balances pH and helps in secretion of toxins out of an organism. Spirulina is the wealthiest source of beta-carotene, 10 times more than carrot. Research shows that beta-carotene is the best nutrient in fight against free radicals. Besides beta-carotene, it also contains zeaxanthin—a powerful antioxidant which has eight times stronger effect than beta-carotene [23]. Zeaxanthin has protective effect on the nervous system, brain, and eyes. Spirulina is very effective against heavy metals and medicine poisoning [24]. In case of those being overweight, it reduces hunger and cholesterol level. It protects pancreas and insulin-producing cells and thus prevents diabetes [25]. Spirulina also blocks interleukin 4 which participates in creation of allergic reaction. Studies have indicated its amazing power in stopping inflammations in the body, what is important for prevention and treatment of arthritis and many other inflammatory diseases. Due to detoxication capabilities, it was used in the Soviet Union after the Chernobyl catastrophe [26]. Having more proteins than meat, it is an excellent supplement in vegetarian and vegan diet [27].

2.7 Burdock (*Arctium lappa*)

Burdock originates from Europe and Siberia, but nowadays it can be found around the world. Burdock's root contains up to 50% of inulins, phenolic acids (caffeic and chlorogenic), and polyacetylenes. Seeds contain about 15–30% of plant oil, bitter glycoside arctiin, arctigenin, and lignans (isolappaol A and lappaol B). Burdock is traditionally used in ulcers, acne, psoriasis, and seborrhea, and it is proven to be effective in skin infections caused by gram-positive bacteria. Due to the abundance of inulins, it has beneficial effect on intestinal microflora, and it helps with regulation of the blood sugar levels. Burdock is also effective as choleretic, and it is the plant of choice for liver drainage [28]. It has anti-allergic and anti-inflammatory effects [29]. People sensitive to Asteraceae should be careful in using it because it can cause allergic reaction.

2.8 Turmeric (*Curcuma*)

Turmeric is a plant from ginger family, mostly grown in South Asia. It is a useful addition to diet and frequently subject, of clinical trials, which has numerous

effects on human organism. It has anti-inflammatory effect; thus it is used in osteoarthritis and rheumatoid arthritis, ulcerous colitis, and gastritis [30]. Useful in prevention of various types of dementia and cancers, it is a powerful antioxidant and helps in healing wounds. Curcuminoids are phenolic antioxidants, and the most important representative is curcumin, found at about 3% in turmeric. Plant also contains sugars, proteins, and some fat. Despite being very biologically active even in very low concentration, the problem with curcumin is its low bioavailability. Very low amount of curcumin is absorbed in the digestive system. Therefore, new product formulas are being developed. Extracts standardized at 95% of curcumin are expanded with piperine, black pepper alkaloid, which increases curcumin absorption; liposomes with curcumin or curcumin aether oil added, that also helps with curcumin absorption. Liposomes are formulated with curcumin or curcumin aether oil added that also helps with curcumin absorption. For centuries, turmeric is used for dyspepsia problem, bloatedness, flatulence, and liver problems. Being choleretic and cholagogue, in modern phytotherapy, turmeric is recommended for difficulties with bile secretion [31]. Therefore, turmeric was an ideal plant for small gallstones problem, but the treatment must be performed under doctor's control. It has antioxidative, hepatoprotective, and antiviral effects [32]. Clinical studies confirm that it protects liver cells from hepatotoxic medicines [33]. Theoretically, there is a possibility of an interaction with coagulation medicines (acetylsalicylic acid, warfarin, heparin, and nonsteroid anti-inflammatory medicines). Extract use is not recommended during pregnancy. Hypersensitivity is possible but very rare. High dosage in sensitive people may stimulate stomach [34].

2.9 Green tea (*Camellia sinensis*)

A study in Japan compared effects of six Chinese teas on liver injuries caused by carbon tetrachloride (CCl_4) and categorized them according to their manufacturing process into green, white, yellow, oolong, black, and pu-erh. Wistar rats were given Chinese tea and afterward intraperitoneal CCl_4 or olive oil. Yellow tea significantly contributed to the protection from liver injury [35]. The difference among types of tea is related to the processing technology, time needed for the leaves to mature, or fermentation level. They have very high anticancerogenic, antioxidative, and anti-inflammatory effects. Green tea has more hepatoprotective effects compared to other types of tea, black tea, for instance. Polyphenol extract of green tea alleviated liver damage and apoptotic, oxidative, and inflammatory changes on the rat liver following hemorrhage/resuscitation [36]. In the case of mice intoxicated with iron, green tea extract reduced iron buildup in the liver, as well as creation of free radicals and oxidative stress [37]. Rats on atherogenic diet [38] or with cadmium exposure [39] had alleviated oxidative stress and liver damage thanks to green tea extract. Clinical trials indicate that consummation of green tea can reduce risk of liver disease in humans [40]. It is known that epigallocatechin gallate, the main catechin in the green tea has a modulation role in various diseases in humans, thus affecting numerous signal pathways. However, using green tea extracts can also have some unwanted effects such as hepatotoxicity, if used in concentrated form [41]. These findings confirm doubt that excessive intake of antioxidants can have adverse effect, i.e., pro-oxidative effect [42].

2.10 Dandelion (*Taraxacum officinale*)

Dandelion belongs to the family of Asteraceae. It comes from Europe and North Asia. Leaves are very tasty and a healthy addition to salads. Dandelion leaves contain a lot of minerals among which there are, in particular, potassium, beta-carotene,

flavonoids, sesquiterpene lactones, taraxinic acid, and sterols. Primarily, it is used as diuretic. It has confirmed choleretic effect. Diuretic effect is significantly lower than in leaves, due to the inulin content which belongs to prebiotic fiber [43]. It has beneficial effect on intestinal microflora, and it helps with regulation of the blood sugar levels. Dandelion is used as bitter tonic for stimulating eating and in case of dyspepsia and fatty liver related to obesity [44]. It is also used in drainage cures. In case of increased cholesterol, cellulite, and weight loss, it is used as additional therapy. There is also a possibility of allergic reactions in sensitive people. It must not be used in people with bile duct obstruction. When there are gallstones, it must be taken under professional supervision. The application with digitalis and lithium preparation is not recommended. In case of gastritis and peptic ulcer, dandelion, just as all other choleretics and draining plants, should be used with caution.

2.11 Pomegranate (*Punica granatum*)

Pomegranate is one of the oldest fruit types. Rich in antioxidants, it is highly appreciated as a symbol of health, fertility, and eternal life [45]. Many studies have confirmed that it is one of the plants with the best healing effects in the world on the cardiovascular, nervous, and skeletal system. Pomegranate is an excellent source of vitamin B5, potassium, and natural phenols like ellagitannin and flavonoids. It contains phytochemicals that provoke creation of serotonin for mood improvement and estrogen for bone mass preservation, which is essential in prevention of osteoporosis. Clinical trials indicate that substances found in pomegranate, known as punicalagins, are beneficial to heart and blood veins health and have anti-inflammatory [46] and hepatoprotective effect in case of toxic liver damage. Punicalagins are also the main source of antioxidative effect. Ingredients in pomegranate inhibit growth of breast cancer, prostate cancer, colon cancer, and leukemia and prevent changes which may cause the growth of tumor [47]. It has estrogenic, anti-inflammatory, and antimicrobic properties. The research suggests that pomegranate oil protects from cancer, diabetes, obesity, and heart diseases. Being rich in antioxidants, pomegranate oil is a powerful ally in fight against aging [48].

2.12 Milk thistle (*Silybum marianum*)

Milk thistle is one of the best plants in protection and detoxication of liver. It can grow up to 2 meters in height, and it is very spiky. In many countries around the world, the plant is registered as herbal medicine. The healing part of the milk thistle is its fruit, i.e., seeds. There are numerous in vitro studies, animal studies, as well as clinical studies performed on humans. However, final conclusions regarding effects and effectiveness of this plant are still not made. What can be said with certainty is that it has hepatoprotective and hepatoregenerative effect while also increasing the level of glutathiones in liver. It does not provoke bile secretion, and thus it is appropriate for the use in cases where classic drainage plants are considered as contraindication. The plant is considered to be nontoxic and appropriate for long-term use, without pauses [49]. It is usually used for alcohol-induced liver damage, fatty liver, nonalcoholic steatohepatitis, and liver damage caused by toxins and medicines and as an auxiliary therapy for chronic hepatitis and liver cirrhosis. However, it is also very helpful in controlling blood sugar and cholesterol levels. In several minor clinical trials, milk thistle did not have any important influence on hepatitis. The treatment of patients with chronic hepatitis C resulted in reduction of serum indicators of liver damage, but without significant influence on viremia [50]. In another research, there was no significant influence on the amount of ribonucleic acid (RNA) of hepatitis C virus in the serum, on the level of ALT or the quality of life [51]. It is indicative that

it can have partially protective effect as inflammatory response in hepatitis C, but it cannot play the role of antiviral agent. The possible cause of the ineffectiveness of herbal extract is probably the result of the fact that the most active components showing hepatoprotective effect are represented in much smaller percentage than if used individually. The use of silymarin resulted in the improvement of clinical symptoms of acute hepatitis, although there was no effect on inflammation process indications [52]. In a number of studies, silibinin, pharmacologically the most active flavonolignan compound in silymarin, significantly improved clinical symptoms and biochemical indications of liver function in acute and chronic hepatitis [53], alcoholic liver disease, and liver damage caused by medications [54]. Silibinin proved to be a very strong inhibitor of human liver stellate cells in vitro. They are considered to be the main producers of extracellular matrix responsible for creation of connective tissue, usually found in liver fibrosis [55]. Silymarin consists of silibinin A and B, isosilibinin A and B, silicristin, and silidianin. Plants contain about 3–6% of these compounds. There are also flavonoids, taxifolin, and quercetol. The fruit contains up to 30% of herbal oil rich in linoleic acid and phytosterols. Active ingredients found in milk thistle are not water soluble, and preparation of tea and brew makes no sense. Tinctures are also obsolete. Current extracts are factory standardized at the silymarin contents of 65–80%, and dosage is determined by the content of silymarin and not by the total volume of extract. Similar to turmeric, the problem is with the resorption of active substances from digestive system. Therefore, silymarin complex bound to lecithin was developed and thus increased its bioavailability for 5–10 times. There are very rare allergic reactions, stomach irritation, nausea, bloatedness, diarrhea, and headache. Due to the lack of data, it is not recommended to be used during pregnancy and breastfeeding. In 2013, Jinnah Postgraduate Medical Center in Karachi conducted a study aimed at the assessment of hepatoprotective role of silymarin against hepatotoxicity induced by isonicotinohydrazide. First group of rabbits was subjected to liver function test without any medicine; second group was treated with silymarin; III group received isoniazid, and IV group received combination of isoniazid and silymarin. There was no case of mortality. Group III had increased levels of bilirubin, and ALT was significantly reduced. Group IV had statistically important improvement in serum bilirubin and ALT. Hepatotoxicity induced by isonicotinohydrazide is well treated with simultaneous application of silymarin [56].

2.13 Common chicory (*Cichorii herba*)

Chicory is a wild plant that usually grows next to fields and roads. It is very popular herb in traditional medicine. Chicory root is rich in inulin and contains about 15% of sugar, some proteins, and cellulose. The most interesting compounds found in chicory are sesquiterpenic lactones, triterpenes, and flavonoids. It is used for problems with digestion, and it has hepatoprotective and anti-inflammatory effects, but also as an additional therapy in reducing high blood cholesterol values [57]. Individual compounds from the plant have proven sedative effect (lactucin and lactucopicrin). Therapeutic use is not recommended during pregnancy. It must not be used in people with bile duct obstruction. There is also a possibility of allergic reactions in sensitive people. In rare cases, there may occur nausea, diarrhea, bloatedness, and gases and use for gallstones must be under professional supervision.

2.14 Bilberry (*Vaccinium myrtillus*)

Bilberry is a deciduous shrub from Ericaceae family with the height of 20–25 cm. It is widely present in pine, spruce, and beech woods. The fruit is a round berry with 5–10 mm in diameter, dark blue colored, with thick skin and acidic-sweet taste.

Conducted research indicates the beneficial effect of blueberries on human cells in the eye retina, brain, and tumor cells [58]. Using animal model, Chinese scientists were testing the effect of blueberries on liver fibrosis. Study results indicate that blueberries can reduce degree of liver damage and the level of hyaluronic acid and ALT in blood. Based on results, authors of the study concluded that blueberries have beneficial effect on liver diseases, oxidative stress, steatosis, and even fibrosis [59].

2.15 Ubiquinone (coenzyme Q1o)

Ubiquinone belongs to the family of compounds called quinones. In 1957, it was for the first time isolated and named ubiquinone due to its wide spread in the nature. It is a substance similar to vitamins which can be found in all parts of the body and has the effect similar to that of vitamin E. However, it is probably a more powerful antioxidant than vitamin E. There are 10 known substances marked as coenzyme Qs, but coenzyme Q10 is the only one that can be found in human tissue. It has crucial role in energy production in every cell of our body. It helps circulation, stimulates immune system, increases oxygenation of tissues, and has significant antiaging effect. Human organism has the ability to synthesize Q10; however, this ability is reduced after the age of 30. The lack of Q10 is also connected to periodontal disease, diabetes, and muscular dystrophy. Belgian scientists from the University of Leuwen discovered another positive effect of coenzyme Q10, i.e., it prevents development of fatty liver related to obesity. Besides being the base for energy production, it also has series of functions with, most frequently, anti-inflammatory effect. A study in Iran indicated that Q10 as a powerful antioxidant prevents LDL from oxidation in vitro and can be a useful alternative for reduction of risk from atherosclerosis, coronary heart disease, and other health issues related to free radicals. While affecting genetic expression in liver, it reduces creation of free oxygen radicals and other "stressful" products, thus diminishing the inflammation in an organism. Q10 is an ideal partner in the fight against atherosclerosis and "fatty liver" [60]. This substance can be found in all living beings, but there are also high concentrations of it in groceries, including nut fruits and oils. There are many food additives that contain Q10.

2.16 Plant *Millettia pulchra*

It is a plant from the family of Leguminosae. It is frequently used in popular folk medicine of China, and its main ingredient is Yulangsan polysaccharide (YLSPS). Being used as a liver protection agent, it is also used as antiaging and memory-enhancing agent. The aim of the study was to search for protective effects of YLSPS against nimesulide-induced hepatotoxicity in mice. Compared to control group, YLSPS significantly reduced activities of ALT, AST, alkaline phosphatase (ALP), and bilirubin content in the serum. Antioxidative effect of YLSPS is the result of increased activity of superoxide dismutase, catalase, and glutathione peroxidase in the liver. Besides the aforementioned, the content of malondialdehyde is reduced, and histological findings were confirmed by antihepatotoxic effect as well. YLSPS showed significant inhibition of pro-inflammation mediators such as tumor necrosis alpha (TNF-α) and interleukin-6 (IL-6). Protective effect of YLSPS in nimesulide-induced liver damage can be achieved thanks to its ability to reduce oxidative stress and prevent nimesulide-induced hepatotoxicity by inhibiting critical control points of apoptosis [61].

2.17 Plant *Atalantia ceylanica*

The extract made from leaves of plant *Atalantia ceylanica* is used in a traditional medicine in Sri Lanka for a treatment of various liver diseases. Lyophilized powder

of watery leaf extract was tested for its phytochemical ingredients, antioxidants, and hepatoprotective activity in vitro. Hepatotoxicity was induced in the pieces of pig's liver to test hepatoprotective activity. Parts of liver were cut off and incubated at 37°C with various concentrations of watery extract of *A. ceylanica* in the presence of ethanol during the period of 2 hours. Hepatoprotective effects are quantified through the transfer of ALT, AST, and lactate dehydrogenase (LDH) into medium [62].

2.18 Liquorice (*Glycyrrhiza glabra*)

Liquorice is a perennial and herbaceous plant from the family of legumes. It grows in the Mediterranean, close to rivers, in sandy and clay ground. The plant can grow up to 2 meters in height. The flower has specific form of Leguminosae, and the crown is yellow-white. The fruit is in the oblong pod, brown in color. Potential therapeutic effect on liver diseases is characteristic of all plants from Phyllanthus family, including *Glycyrrhizin glabra*. *Phyllanthus fraternus* indicated protective effect against dysfunctional mitochondria induced by bromobenzene in rat's liver mitochondria [63]. The extract of Phyllanthus prevented hepatotoxicity, induced by acetaminophen, by inhibiting cytochrome P459 CYP2E158. In rat's hepatocytes, phyllanthin, active ingredient, prevented intracellular growth of ROS and lipid peroxidation [64]. The extract *Phyllanthus urinaria* alleviated steatohepatitis in mice and in the culture of hepatocytes, reducing lipid buildup [65]. The extract Phyllanthus polyphyllus indicated antitumor effect in mice and human tumor cell lines MCF7 (breast cancer), HT29 colon cancer, and HepG2 (liver cancer) [66]. The lack of relevant clinical trials prevents making any conclusions on hepatoprotective effect of plants from this family. Nevertheless, rare research on patients showed that *Phyllanthus amarus* is not effective in the treatment of viral hepatitis [67], whereas glycyrrhizin a triterpenic ingredient in *Glycyrrhizin glabra* successfully reduced HCV titer in vitro [68]. In combination with interferon, glycyrrhizin showed synergic effect. Hepatoprotective effect of glycyrrhizin is related to preventing changes in cell membrane permeability. [69]. Glycyrrhetinic acid has protective effect against liver damage induced by hepatotoxic alkaloid resorcin and galactosamine [70]. In cholestatic model of liver damage, glycyrrhizin showed proaptotic effect, whereas glycyrrhetinic acid performed as powerful inhibitor of apoptosis and necrosis induced by bile acids [71]. The results of recent research indicate that glycyrrhizin prevents ischemic-reperfusional liver damage by inhibiting high-mobility group box 1 (HMGB1) early mediator of inflammation [72]. Intravenous application of Stronger Neo-Minophagen C (SNMC), a Japanese compound, containing 0.2% of glycyrrhizin, 0.1% cysteine, and 2% glycine, stopped disease progress in patients with acute seizure of autoimmune hepatitis [73]. Similarly, Korenaga et al. showed in the mice model that SNMC reduces oxidative stress and liver steatosis provoked by combination of HCV and iron [74].

2.19 Plant *Picrorhiza kurroa*

This plant is one of main forest products in Nepalese Himalaya, where it is known as Kutki. It is located far from the community, and it takes a few days walk to get to its habitat. Plant's root has long history of use in Indian Ayurvedic medicine in the digestive problem treatment. Some other uses are also suggested (asthma, liver damage, wound healing, and vitiligo); however, medical results are still not conclusive. It appears that the safe usage is based on the long history of traditional use. Kutki has hepatoprotective features. It is used for all forms of liver damage, cirrhosis, and liver inflammation. It also protects liver from damage caused by hepatitis C virus [75]. Picroliv, an iridous glycoside mixture purified from the plant,

normalized indicators of acute liver damage induced by ethanol [76] and aflatoxin B1 in rats [77]. Picroliv has also effectively prevented hepatocarcinogenesis induced by N-nitrosodiethylamine, hyperlipidemia, liver steatosis, and lipid mobilization from adipose tissue in rats treated with hydrazine [78]. In rats chronically intoxicated with cadmium, picroliv alleviated pathological changes in liver and kidneys. Picroliv was also more successful at alleviating pathological changes in liver of rats intoxicated with galactosamine than its two most known ingredients picroside and kutkoside individually [79].

2.20 Barberry (*Berberis vulgaris*)

Barberry was traditionally used in the treatment of various liver diseases. Common barberry is a shrub originating from Central and Southern Europe, Northwestern Africa, and Western Asia. It grows as a deciduous bush covered in thorns and with yellow color under the bark. The fruit is a long oblong red berry and sour, containing 2–3 seeds in the inside. Berries are edible and rich in vitamin C but very sour and hard to reach because of thorns. Berberine, alkaloid isolated from plant, is one of interesting compounds which is controversial because of its toxicity in experimental animals. Thus, lethal dose in intraperitoneal application in mice was 30 mg/kg [52, 58] and 205 mg/kg in rats [54]. Research on human subjects showed good resistance, even when it is consumed in high dosages for prolonged time period. Patients with diabetes type 2 and weakened liver function managed to successfully reduce the level of glucose in blood and diminish liver damage thanks to the use of berberine without significant side effects [80]. Treatment with berberine improved liver function and alleviated signs of dyslipidemia in hyperlipidemic patients with hepatitis C and liver cirrhosis and in patients with diabetes type 2 [81]. Research conducted on 1751 dyslipidemic patients showed improvement of lipid status in blood, with significant reduction of total risk of cardiovascular diseases [82]. Just in case, berberine should be avoided during pregnancy because it can cause jaundice and fetal kernicterus [83].

2.21 Nigella (*Nigella sativa*)

Nigella and more than 20 names are related to the miraculous plant which is used for over 3000 years. It is mentioned in the Bible as black cumin. The usefulness of this plant was also described by the Prophet Mohammed s.a.w.s. in words: "Nigella contains in itself the remedy for all diseases except death." Hippocrates in his logs writes about effectiveness of this plant in healing digestive problems. In Ancient Greece, it was known as the agent for strengthening in case of physical and mental weakness of the patient. Nigella is an annual flowering plant, native to South and Southwest Asia. The fruit is a large and inflated capsule, each containing numerous seeds. Seeds are used as spice and replacement for black cumin. Seeds used for preparation of nigella oils, in large quantities, usually come from Egypt, Syria, India, Pakistan, or Ethiopia. Nigella oil is produced by so-called cold squeezing, and it is not subjected to further manipulation. What was traditionally a feature of Nigella oil, biomedicine started to confirm only since 1964. Until today, there are over 460 researches which prove its benefits for human health. The oil has beneficial effect on over 40 health conditions and more than 20 pharmacological effects. It acts as analgesic, as antibacterial [107], as anti-inflammatory, as antiulcerous, as anticholinergic, against high blood pressure, as antioxidant, as antiasthmatic, as antiviral, as bronchodilator, as antidiabetic, as hepatoprotective [84], against low blood pressure, in inulin synthesis, as antagonist to white blood cells, and as kidney protector. The oil is rich in linoleic acid, thymoquinone, nigellone, melanthin,

nigellinine, damascenine, and tannin. It has been discovered that oil also contains beta-sitosterol, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, folic acid, and arachidonic acid. Besides the aforementioned, it is also rich in proteins; vitamins B1, B2, B6, C, and E; calcium; iron; copper; zinc; and phosphorus. Storage, squeezing, and preservation of nigella oil are very important because, in inappropriate conditions, it can have toxic effect [85].

2.22 Coumarin

Coumarin is a chemical compound found in many plants, especially in tonka seeds, woodruff, sweet grass, Perforate St John's-wort, strawberries, apricots, cherries, cinnamon, and sweet clovers. Coumarins can be found in large quantities in some oils, especially cinnamon oil, Chinese cinnamon leaf oil, and lavender oil, and in herbs like chicory, and in highest quantities in plants from the families Rutaceae and Umbelliferae [86]. There are plenty known derivatives of coumarin, synthetic or natural, and such structural diversity is the cause for many various biological activities. IMUNOMAX is dietary supplement which contains extracts of plants rich with 4-MU for liver regeneration, but it also has broad spectrum of other effects. In the world, it is considered as the strongest booster of the immune system: increases the number of T cells and the activity of NK (natural killer) cells by 300–800%, activates the immune cells (NK, LAK, and macrophage), increases cytokine production (TNF-a, gamma interferon IL-2, and IL-12), inhibits immunosuppressive cytokines like TGF-b, improves Th1/Th2 balance, and improves the function of cytotoxic white blood cells. Boosting immunity, it prevents the transition from acute into chronic form of disease, shortens disease duration, and prevents possible complications [87]. Due to immunomodulation features, there is also a possibility of its application in the treatment of chronic infectious and opportunistic infections, in brucellosis treatment [88], MRSA infections [89], for antimicrobial activity in digestive tract [90], and for antifungal activity, and some coumarins also show tuberculostatic activity. Research at the University of Texas (San Antonio) from 2005 to 2007 involving 160 patients showed that 4-MU can stop and reduce symptoms and complications of chronic virus infection with hepatitis B (HBV) and hepatitis C (HCV). This effect was noticed with naive patients, as well as with those who did not react to interferon, which was earlier used as first-line therapy for HBV and HCV infections. It is assumed that 4-MU slows down progression of hepatitis into cirrhosis and liver cancer [91]. Research into coumarin metabolism proved that rats are not suitable model for research into toxicity of coumarin for humans [92]. Coumarins generally display multiple biological activities: anticoagulative, estrogenic, photosensitive, antimicrobial, vasodilatative, antiviral against HBV and HDV [93] and HCV, and molluscicidal activity; they act as anthelmintic (in digestive system) and as sedatives and hypnotics and also indicate analgesic and hypothermal effects. Other biological activities include inhibition of aggregation of platelets, cytochrome P450 and steroid 5α-reductase, spasmolytic, choleretic [94], anticancerogenic and anti-HIV activities [95], diabetes type 1, multiple sclerosis, Alzheimer's disease, and rheumatoid arthritis. It also shows excellent effectiveness in removal of radicals, i.e., antioxidation mechanisms. Disease prevention and antioxidative features are also very important [96]. 4-MU is a powerful inhibitor of hyaluronic acid synthesis, and the result is antitumor effect; thus it can be used as chemotherapeutic agent in prostate cancer [97], breast cancer [98], stomach, melanoma, and renal cancer and prevents and helps in treatment of hepatocellular cancer [99]. Prevention and treatment of advanced prostate cancer with nontoxic agent alleviates side effects of oncological treatment, and it can also improve outcome while preserving life quality. 4-MU does not react directly with cancer itself.

It boosts immune system to be able to do its primary task—destroy tumor cells! This also explains why the compound is so effective with other types of cancer (lungs, stomach, colon, thyroid gland, ova, testes, tongue). Results are ranked from real reduction in tumor mass to stopping of growth of tumor, preventing the spread of metastases, increasing survival times, and improving of life quality during disease [100]. There are no recorded negative side effects during this therapy nor interactions with other medications. On the contrary, it is considered as an effective agent for relieving unpleasant side effects of drugs, including toxic chemotherapeutics.

3. Mechanisms of action of phytochemicals

Medicinal herbs, as a part of alternative strategy for disease prevention, which are traditionally used in folk medicine, it become important factors in human health preservation. Natural compounds with pharmacological effects for humans come into numerous interactions with internal and external cell molecules. A huge number of potential mechanisms of action of phytochemicals are suggested as a treatment for different diseases, including liver diseases. They are also independent of antioxidative activities [101]. Experiments on animals and cell cultures indicate that natural compounds can reduce pathological changes in the liver. Plants contain numerous phytochemicals: Polyphenols, phenol acids, coumarins, stilbene, tannins, lignans, and lignins [102, 103]. Polyphenols are the most famous micronutrients found in abundant amounts in diet, alongside with fruit and drinks, such as tea and red wine, as their primary source. Health effects of polyphenols depend on the amount consumed and their bioavailability. Flavonoids are the most widely spread polyphenol compounds found in plants. They can be divided into several groups: flavane, flavone, flavonol, flavanone, flavanonols, isoflavonoids, and anthocyanidins [104]. Polyphenols are proven to display a broad spectrum of pharmacological effects: Flavonoids show antiallergenic [105], anti-inflammatory, antidiabetic, cardioprotective [106], vasoprotective [107], neuroprotective [108], hepatoprotective [102], gastroprotective [109], antiviral [110], and anticancerogenic effects [111]. Flavonoids are also potential inhibitors of cellular autoimmunity [112]. Many of these compounds act as regulators of internal cellular processes such as cellular signalization or appropriate gene expression [113]. Molecular protection mechanisms and polyphenol treatment activity in different pathological conditions cannot be ascribed exclusively to their antioxidative effect but also to direct blocking of signal pathways. Anthocyanins, a type of flavonoids, for instance, affect the activity of more than 120 receptors, signal molecules, transcription factors, and genes while directly reacting with more than 20 molecular targets. Their activity depends on structure, whereas their antioxidative potential does not necessarily correlate with their ability to affect internal and external cellular processes [113].

3.1 Free radicals

Free radicals are compounds that are natural products of metabolism. Many of them have important physiological role (nitrous oxide and superoxide radical). However, increased production results in damage to the protein molecules, lipids, and genetical material. Radicals' production in an organism is incurred by numerous factors from the environment, toxic agents, polluted air, smoking, sun exposure, chronic diseases, infections, cancerogenic substances, intensive exercise, and genetic presupposition [101, 113]. Free radicals, along with other highly reactive compounds originating from oxygen, belong to the group of reactive oxygen species (ROS). ROS are result of all the processes that include the exchange of electrons,

and the most frequent causes are respiratory chain in mitochondria, endoplasmic reticulum (reaction to cytochrome P 450), hemoglobin oxidation in red blood cells, special cells (leucocytes, macrophages, and others create superoxide through NADPH oxidase), and external factors (UV light, X-rays, toxic chemicals, aromatic nitrous compounds, etc.) [102].

3.2 Antioxidants

Antioxidants are a group of different compounds acting as a protection from harmful effects of free radicals. They are provided in food, like vitamins and minerals. However, many of them are produced in the organism as well. They can be of enzymatic (catalase, SOD) and nonenzymatic origin (glutathione and vitamins C and E) [102]. Free radicals are neutralized in numerous ways: By binding with pro-oxidative metal ions (iron and copper), by removing reactive compounds of oxygen (superoxide radical and hydrogen peroxide), and by inhibiting enzymes that create free radicals (NADPH oxidase). Their effects are related to slowing down aging process; reduction of cholesterol levels; reduction of risks of atherosclerosis, cardiac arrest, and stroke; prevention of creation and growth of tumors; and protection from other pathological conditions. Nowadays, various herbs and herbal preparations and medicines are more and more used in prevention and protection from liver diseases. Their most important function is antioxidative effect. Recently, significant amount of attention was dedicated to medicinal herbs with antioxidative effects [101].

4. Conclusions

Medicinal herbs, if used properly, have almost no unwanted effects, and if there are some, they are reduced to minimum. Nowadays, farming medicinal herbs without the use of artificial fertilizers and insecticides and in ecologically clean areas is preferred, in order to avoid harmful effects of pollution. Controlled picking, preservation, and processing ensure plants' health safety. Medicinal herbs are used in various pharmaceutical forms: water extracts of herbal drugs (infusions, decocts, macerates), ethanol tinctures, oil macerates, syrups, and capsules and pills. The substances important for plant's effect are very often in only one part of the plant, and thus this part in particular is used as herbal drug. Contemporary phytotherapy is a perfect combination of traditional experience and the results of modern science. Nowadays, chemical composition of the main effective substance is usually known, and the use of medicinal herbs should be rationalized and left to experts. This is particularly important when combining medicinal herbs and in using with other medicines. FDA has standards for preparation of all food supplements including medicinal herbs. FDA requires that ingredients listed on the label must actually be in the product itself, and there should be no harmful toxins, such as pesticides, for instance. FDA does not allow statements with medical indications or claims for any herbal preparation, even when its use is scientifically proven. Medicinal herbs and food supplements can have labels predicted for the category of functional food. These claims are referred to supporting body functions, for instance, that ginkgo contributes to brain health. Dietary supplements (DS) in the USA are regulated by several federal agencies whose jurisdictions overlap, Food and Drug Administration (FDA) and Federal Trade Commission (FTC), enforced by Attorney General Office (AGO) and Department of Justice (DOJ), and monitored by Center for Disease Control (CDC). FDA can remove DS from the market should there be report on unwanted event, due to contamination, misidentification, false listing, or claims and if they do not comply with Good Manufacture

Practice (GMP). FTC and AGO can enforce laws against deceiving marketing practices. Suggested improvements of existing regulatory demands are included in online DS toxic tables in a series, in order to warn in advance consumers, clinics, corporations, and governments of possible serious side effects. They can also accelerate the response rate during oversight of marketing phase IV which would enable government to have its regulatory jurisdiction [114].

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