

The therapeutic importance of herbal materials in liver diseases

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S u m m a r y

The liver is one of the major organs of the human body which plays an important role in the detoxification of xenobiotics, among which are mentioned alcohol, stimulants, drugs. The parenchymal cells of the liver called hepatocytes which have high ability to regenerate, are a main component of this organ. There are many factors that damage the liver e.g. drugs, chemicals, viral infections, autoimmune processes, metabolic disorders. These factors have a significant effect on the proper function of hepatocyte. In the treatment of liver diseases besides medicaments, a lot of meaning has diet as well as phytotherapy that is treatment with use of herbal preparations. The most commonly used substance is silymarin extracted from milk thistle (*Silybum marianum*).

Key words: *phytotherapy, liver diseases, herbal materials, silymarin*

INTRODUCTION

The liver is the main organ involved in detoxification of a variety of xenobiotics that aren't normally produced or consumed by the organism. The parenchymal cells called hepatocytes which have high ability to regenerate, are a main component of this organ while the hepatic lobule is a basic morphological and functional unit. The liver as one of the most important organs in the human body is responsible for many functions among which are mentioned:

- protein synthesis (albumin, globulin except immunoglobulins, prothrombin, fibrinogen, angiotensinogen)
- production of bile
- production and storage of enzymes
- regulation of metabolism (carbohydrates, amino acids, fatty acids, hormones)
- neutralization of toxins
- metabolism of alcohol and drugs
- regulation of blood glucose levels
- storage of iron and certain vitamins (A, D, K, B₁₂)
- participation in thermoregulation
- participation in the immune system
- regulation of the production of cholesterol
- regulation of hemostatic processes (synthesis of plasma clotting factors)
- action of hematopoietic (in newborn) [1, 2].

There are many factors that can damage the liver, e.g. chemical substances (alcohol, carbon tetrachloride), mushrooms toxins, drugs (antibiotics, nonsteroidal anti-inflammatory drugs - NSAIDs), high dose vitamin A, estrogens (tab. 1). Moreover, the inflammatory processes including autoimmune diseases and metabolic disorders also have a damaging effect on the liver. Most of these factors is associated with slowing of metabolic processes carried out by the cytochrome P450 enzymes that are responsible for metabolism of a variety of xenobiotics (drugs, carcinogens, food components) as well as the synthesis of endogenous compounds (hormones, leukotriens, prostaglandins) [3-6].

Although the liver is an organ having a large functional reserve and regenerative capacity, it is constantly exposed to action of the harmful factors that can lead to structural changes in the form of steatosis, fibrosis or cirrhosis of the whole organ. Alcohol is mostly cause of steatosis. Its abuse leads to increased influx of free fatty acids and abnormal β -oxidation leading to accumulation of fat droplets in hepatocytes (diabetes, obesity). Among the factors that cause fatty liver are mentioned: tetracycline, amiodarone, camphor, aflatoxins, metabolic disorders (e.g. Niemann-Pick disease) and phospholipid storage disorders [3, 6].

Another type of liver injury is fibrosis of this organ. This involves with the accumulation of collagen type I and III in the parenchyma of the liver. This phenomenon occurs in case of alcoholic hepatitis, hepatitis B, C and D, narrowing of the

bile duct, primary fibrosing cholangitis, schistosomiasis and the rejection of the transplant. The final stage of many liver diseases is cirrhosis that leads to a reconstruction of the correct architecture in the fiber-nodular organ. Another common case occurring in patients is gallstones which can also be an indirect cause of the appearance of cirrhosis [7]. Both cirrhosis and chronic liver failure can lead to causes of morbidity and mortality. However, the proper treatment may prevent or slow the progression of the disease as well as to prevent complications. Often it is required close monitoring of therapy and proper diet. Furthermore, it is prohibited from receiving alcohol and hepatotoxic drugs (e.g. derivatives of phenothiazines, thiazides, tetracyclines, macrolides) [3, 5, 6].

Table 1.

The most common groups of xenobiotics that may cause toxic liver damage [3, 5, 6]

groups of xenobiotics	examples
drugs	<ul style="list-style-type: none"> • antilipidemics (statins, clofibrate, ezetimibe) • antidiabetics (rosiglitazone) • antivirals (ribavirin, efavirenz, nevirapine) • tuberculostatics (isoniazid, rifampicin) • antifungals (fluconazole, ketoconazole) • antibiotics (amoxicillin, cephalosporins) • antiparasitics (albendazole) • antineoplastics (L-asparaginase, azathioprine, cyclophosphamide) • NSAIDs (ibuprofen, diclofenac, ketoprofen) • antihypertensives (methyldopa, lizinopril) • rheumatologics (allopurinol) • others (oral contraceptives, halothane)
industrial chemicals	<ul style="list-style-type: none"> • phosphorus • herbicides • vinyl chloride • barium salts
auxiliary products, pharmaceuticals based on herbs	<ul style="list-style-type: none"> • Kava kava • pyrrolizidine alkaloids • Ma Huang (ephedra) • Camphor • Chinese herbs
other xenobiotics, food poisoning	<ul style="list-style-type: none"> • ethyl alcohol • mushrooms (alpha-amanityna) • mycotoxin of peanuts (aflatoxin)

An alternative to drug therapy is treatment with use of herbal preparations which naturally regenerate and support the liver. The importance of natural medicine, especially phytotherapy in modern medicine is widely known and described in numerous publications. Equally often, reports concerning the use of herbal materials in hepatotherapy are published [8].

Herbal materials used in the treatment of liver diseases

Phytotherapy, or treatment of herbal materials, still plays a huge role in modern medicine. It involves the use of herbal remedies to treat various diseases and their prevention.

Besides medicinal properties, the herbal preparations also have a protective effect during therapy with drugs damaging parenchymal organs. Most of the currently used synthetic drugs have the nephrotoxic and hepatotoxic action. Co-administration of herbal extracts containing cytoprotective substances may increase the therapeutic activity of these drugs and reduce drug-induced damage [9].

The purpose of this paper is to draw attention to the herbal materials which play an important role as drugs or adjuvants in various liver diseases. These are mainly of artichoke leaves (*Folium Cynarae*), Chinese Schizandra fruit (*Fructus Schisandrae*) and milk thistle fruit (*Fructus Sylibi Mariani*).

Sylibum marianum (L.) Gaertner

Milk thistle (family *Compositiae*) is one of the oldest plants used in hepatotherapy derived from the Mediterranean area. Its contains flavonolignans such as silybin, silychristin, silydianin and izosilybin defined generic name silymarin. The most active component of this complex constituting 60-70% is silybin. Its structural similarity to steroid hormone gives the ability of silymarin to stimulate protein synthesis. Milk thistle seed extract contains over 70% silymarin that delivers several health benefits [10].

According to the literature, silybin has a regenerative and protective effects on hepatocytes against organic and inorganic compounds (e.g. alcohol), mushroom toxins and others. Currently, silymarin or silybin is used to treat cirrhosis, chronic hepatitis, jaundice and diseases caused by excessive alcohol consumption, poisoning of amatoxins or phalotoxins [11, 12]. The mechanism of hepatoprotective action is multidirectional because it is associated with stimulation of synthesis of ribosomal RNA (stimulation of polymerase I and rRNA transcription), protection of cell membranes from damage by free radicals, stabilizing cell membranes, blocking the binding of toxins as well as increase in the expression of certain genes in the liver (e.g. TGF β 1 and c-myc) [13]. Besides the cytoprotective activity, silybin has antioxidant effect and acts against free radicals. It was shown that this compound also has the potential to inhibit and modulate the activity of drug transporters, estrogenic receptors and nuclear receptors [9, 10].

Clinical studies of patients with liver diseases indicate that the extract of this plant causes an increase of superoxide dismutase activity in lymphocytes and erythrocytes as well as increase of glutathione and glutathione peroxidase levels. Furthermore, it was shown that silymarin at a dose of 420 mg/24 h normalizes the levels of AST, ALT, bilirubin, GGTP in patients with different diseases of this organ

with the exception of hepatitis. However, some authors suggest that silymarin has anti-inflammatory and regenerating effect in some types of hepatitis [11, 12].

In other studies, it was also shown that silymarin doesn't affect the microsomal enzymes in the pathologically unchanged liver with the exception of some cytochrome P450 enzymes. In addition, it was claimed that the milk thistle extract is practically devoid of side effects. There was only observed a few cases of hypersensitive reaction, such as headaches, allergic skin rashes, nausea, arthralgia. Furthermore, silymarin has choleric properties to support liver function therefore it is so widely used.

Silymarin and its major active component that is silybin as hydrophilic substances are poorly absorbed from the gastrointestinal tract because of their limited miscibility with lipids and penetrate into the intestinal enterocytes. To increase the bioavailability of silybin in the pharmacological and clinical experiments, Kidd and Head recommend application of combination of this compound with phosphatidylcholine in the form of so-called phytosome [14]. Besides hepatoprotective action, silymarin and silybin have anticancer, carcinogenic and chemoprotective properties. Their activity was also demonstrated in relation to cancers of skin, prostate, lung, CNS, kidney, pancreas and other organs [15-20]. It is understood that mentioned activity is partly modulated the cytoprotective action of silymarin or silybin.

Moreover, Wilasrusmee et al. described a new effect of milk thistle. *In vitro* model they showed that the extract of *Silybum marianum* is immune. The authors have studied standardized extract of milk thistle in a murine lymphocyte proliferation assay using concanavalin A as a mitogen to stimulate non-specific and mixed lymphocyte culture (MLC). They found that the tested extract increased cell proliferation in both assays, and that this effect is connected with an increase of interferon- γ and interleukins (IL-4 and IL-10) in MLC. This study showed that observed immunostimulatory effect of milk thistle may be important in increasing resistance to infectious diseases [21].

Cynara scolymus L.

The second most common use of herbal material in the liver diseases is the artichoke (*Cynara scolymus* L., family *Asteraceae*). This plant probably comes from Ethiopia. The fresh or dried leaves of *Cynara scolymus* are a medicinal raw material. The most important bioactive constituents of artichoke are cynarin, luteolin, cynardoside (luteolin-7-O-glycoside), scolymoside and chlorogenic acid. Cynarin reducing cholesterol production is most concentrated in the leaves [9, 22].

The healing properties of raw material have been confirmed recently, even though the artichoke has been used for centuries in folk medicine to treat liver diseases and disorders of gastric secretory function. Clinical and preclinical studies have confirmed the therapeutic properties of this plant, especially in hypercholesterolemia, digestive disorders and irritable bowel syndrome [9, 10, 22, 23]. Currently, the raw

material is used for the production of medicinal preparations in liver failure, inflammation of the gallbladder, cholangitis, cholelithiasis and disorders of lipid metabolism. Furthermore, it was shown that extracts from artichoke leaves indirectly reduces hepatic cholesterol biosynthesis in a manner beneficial physiologically [24].

***Schisandra chinensis* L. (Turcz.) Baill**

Another plant used to treat liver diseases is *Schizandra chinensis* (*Schisandra-ceae*). This plant is cultivated in the Far East (China, Korea) and countries of Eastern Europe (Ukraine, Bulgaria). The fruits and seeds of *Schizandra chinensis* have numerous compounds such as dibenzocyclootadiene lignans (in the seeds from 7.2% to 19.2%), among which are mentioned schizandrins and schizandrols [25]. Schizandrins are one of the main dibenzocyclooctadiene lignans present in the fruit of this plant.

The main compound of the mixture, which is active in the treatment of viral hepatitis and toxic effects of liver inflammation, is schizandrine B. This compound has the ability to prevent liver damage induced by carbon tetrachloride because stimulates the activity of glutathione reductase and causes the increase of reduced glutathione level in the liver [26]. It also possesses antioxidant properties and stimulates the cytochrome P450 enzymes. In addition, schizandrine is the promoter of important metabolic processes e.g. proteins and participates in the process of gluconeogenesis.

The greatest value of digestible has infusion from *Schizandra* fruit. It is also used in the states of physical and mental fatigue and depression. It is noteworthy that one of the dibenzocyclootadiene derivatives called gomisin G has antiviral activity against HIV as well [22, 27, 28].

Other plants with the hepatoprotective activity

Taxus yunnanensis, which belongs to the plant family *Taxaceae*, has been used in traditional Chinese medicine for the treatment of kidney problems and diabetic conditions. The studies have reported that it also possesses the hepatoprotective action. The major components of the wood of *Taxus yunnanensis* are lignans, secoisolariciresinol and isotaxiresinol [29]. It was shown that aglycone called secoisolariciresinol inhibits the apoptosis of hepatocytes induced by TNF α and inhibits the release of TNF α as well as IFN- γ in activated macrophages [30].

Species of the genus *Phyllanthus* (*Euphorbiaceae*): *P. amarus*, *P. multiflorus*, *P. tenellus*, *P. virgatus* are described as medicinal plants with anti-inflammatory, antiviral antihepatotoxic and hypoglycemic effect. These plants contain lignans, including nyrantine and hinokinin that exhibit the strong inhibitory effect of surface antigen expression of HBsAg and HBeAg. In the Far East, the extracts of these plants are

used to treat hepatitis B and C. They inhibit the activity of HBV DNA polymerase that is an enzyme required to its replication. The most commonly used raw material is herb *Phyllanthus amarus* (grown in India and Ceylon). Furthermore, the extract of *Phyllanthus amarus* is an ingredient of the preparation called Silimar next to milk thistle, *Inula racemosa* root, rhizome of turmeric (*Curcuma longa*) and leaves of *Andrographis paniculata*. It was found that this preparation has a favorable effect of crushing gallstones [27, 30-32].

Another plant is a *Scutellaria baicalensis* (*Labiatae*). Separated from this plant of the compound called wogonin strongly inhibits the production of HBV surface antigens (HBsAg, HBeAg) while the second component - flavone (baicalein) was given in viral hepatitis. Currently, it is suggested that baicalin and baicalein inhibit the antioxidative stress occurring in inflammation and protect against fibrosis in HCV infection [30].

The support action in the treatment of liver diseases also have celandine herb (*Herba Celandine*), yarrow (*Herba Millefolii*), burdock root (*Radix Bardanae*), inflorescentia *Helichrysi*. In their composition there is a high content of manganese, iron, sodium and potassium. Manganese and iron are elements that play an important role in the process of oxidation and reduction by action on the cellular and extracellular enzymes as cofactors. Often damaged liver cells do not metabolize as quickly and efficiently therefore the biological active compounds contained in these herbs can help in action of this organ. In liver diseases particularly in chronic liver failure it is concluded the occurrence of hypokalaemia and hyponatremia which can alleviate giving patients infusions of these herbs such as burdock root infusion (high content of potassium) [33, 34].

Flavonoids contained in *Bidens bipinnata* L. (*Asteraceae*) have a potent hepatoprotective effect in carbon tetrachloride poisoning. They reduce significantly the level of alanine and aspartate transaminase, hyaluronic acid, hepatic hydroxyproline and slows the reduction processes of fatty acids [28]. Furthermore, an extract from the terrestrial part of *Pergularia daemia* (*Asclepiadaceae*) has also positive effect on liver cells in the toxic damage of carbon tetrachloride [35]. Moreover, a lot of medicinal properties is in the alkaloids derived from *Fumaria* India Pugsley (*Fumariaceae*). It was claimed that a dose of 10-20 mg of the isolated extract has such as a potent hepatoprotective action as 25 mg per os of silymarin [36].

CONCLUSIONS

In this paper, it was presented the hepatoprotective and antiviral activity of herbal materials. However, the widespread use of phytotherapy in medicine requires more detailed information concerning the influence of combining these drugs for safety and pharmacological efficacy. Since it should be excluded the possibility of occurrence of hepatic metabolism disturbances during use of both herbal preparations with synthetic drugs.

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ZNACZENIE LECZNICZE SUROWCÓW ROŚLINNYCH W CHOROBYCH WĄTROBY

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Streszczenie

Wątroba jest jednym z najważniejszych narządów ludzkiego organizmu pełniącym istotną rolę w procesie detoksykacji ksenobiotyków, do których należą alkohol, używki, leki. Głównym składnikiem miąższu są komórki wątrobowe zwane hepatocytami mające dużą zdolność regeneracji. Istnieje bardzo wiele czynników uszkadzających wątrobę, np. leki, substancje chemiczne, infekcje wirusowe, procesy autoimmunologiczne, zaburzenia metaboliczne. Czynniki te w istotny sposób wpływają na prawidłową funkcję hepatocytu. W leczeniu schorzeń wątroby poza lekami współczesnej terapii istotne znaczenie ma dieta oraz fitoterapia, czyli leczenie preparatami roślinnymi. Powszechnie stosowaną substancją jest sylimaryna pozyskiwana z ostropestu plamistego (*Silybum marianum*).

Słowa kluczowe: *fitoterapia, choroby wątroby, surowce roślinne, sylimaryna*