**Engilen: from different therapeutic possibilities to effective clinical use**

N. B. Gubergrits, N. V. Byelyayeva, A. Ye. Klochkov, P. G. Fomenko, G. M. Lukashevich
*Donetsk National Medical University (Lyman)*

**Key words:** phytohepatoprotectors, silymarin, inulin, curcumin, Engilen, chronic cholecystitis, non-alcoholic steatohepatitis, dysfunction of the gallbladder

> *The disease is a curative remedy of nature itself in order to eliminate the disorder in the body; therefore, the medicine comes only to the aid of the healing power of nature.*
>
> Arthur Schopenhauer [22]

Currently, the pharmaceutical market of Ukraine presents a wide range of hepatoprotectors, which determines the need for a clear understanding of the advantages and disadvantages of each of them, as well as awareness of the features of their clinical use. Most hepatoprotectors used in clinical practice (almost 80%) are of plant origin, that is, they are phytohepatoprotectors (PhytoHP) [4, 9, 35]. This feature can hardly be called accidental, because PhytoHP has a number of advantages over synthetic drugs (Fig. 1) [1, 8, 20, 21, 26, 33].


**Fig. 1. Benefits of PhytoHP.**

The use of PhytoHP allows you to adhere to the basic principle of treatment of liver pathology — minimizing exotoxic effects [12]. The metabolism of most synthetic drugs, involving the participation of the cytochrome P450 system, is often accompanied by a change in the metabolism not only of the synthetic hepatoprotector, but also in parallel with prescribed drugs. PhytoHPs are more related to the human body, therefore they provide the maximum sparing of the liver [4, 12].

Moreover PhytoHP, as a rule, have a complex pharmacological action; in addition to hepatoprotective properties, they are characterized by antimicrobial, anti-inflammatory, antispasmodic, choleretic, antioxidant, and immunomodulating activity. Thus, the PhytoHP affects several pathogenetic links of liver disease and, in some cases, comorbidities [10, 25].

Herbal hepatoprotectors are characterized by relatively high bioavailability; therefore, cases of overdose and intolerance in their use are rarely observed, as well as the occurrence of side effects. An interesting feature — the ability of active substances to accumulate (for example, silibinin) in hepatocytes — allows you to maximize the therapeutic effects of drugs [4, 10].

The "softness" of the action, safety, and good tolerance make it possible to prescribe PhytoHP on an outpatient basis, to children and the elderly. Biologically active substances in herbal preparations are contained in optimal quantities and ratios, potentiating each other, are easily absorbed by the body, and are means of pathogenetic and symptomatic therapy [17]. The therapeutic effect in the appointment of PhytoHP is resistant, although it is achieved for a longer time than with the treatment with synthetic agents. This justifies the expediency of long courses of treatment with herbal preparations (3–4 weeks or more) [4]. An important advantage of PhytoHP is the advantageous pharmacoeconomic characteristics of these drugs [10, 11, 30].

Despite the many advantages listed above, PhytoHP has some drawbacks:

- pharmacodynamics and pharmacokinetics of these drugs is rather difficult to study;
- lack of etiotropic action;
- likelihood of allergic reactions;
- lack of clear boundaries of their application;
- small amount of evidence-based research;
- do not meet the requirements for the "ideal" hepatoprotector (like many synthetic hepatoprotectors) [9].

**Phytohepatoprotectors: in search of an "ideal" drug**

PhytoHP can be divided into monocomponent (Karsil, Legalon, Silibor, Hofitol, etc.), combined (Engilen, Gepabene) and multicomponent (LIV-52, Galsten) drugs [14, 19, 23, 27, 28]. In our opinion, the use of combined agents is pathogenetically justified, since 2–3 active ingredients logically complement and potentiate the action of each other, providing an optimal and reasonable range of indications. With the use of multi-component preparations containing many different active compounds (for example, LIV-52), and, therefore, with a large number of effects, the likelihood of undesirable actions is higher, which is accompanied by an increased risk of intolerance. The range of therapeutic action of monocomponent drugs is extremely narrow compared with the combined means.

One of the most effective combined PhytoHPs with choleretic properties is Engilen [29]. The preparation consists of three components: 140 mg of dried extract of milk thistle fruit (Silybum marianum; which corresponds to> 80% silymarin) is contained in one capsule; 200 mg of dry artichoke leaf extract (Cynara scolymus L.; active ingredient — cinarin); 25 mg of dry extract of turmeric rhizomes long (Curcuma longa L.; the share of curcumin exceeds 30%).

***Milk thistle (Silybum marianum)***

Milk thistle (frog, sharply-motley) has been used in medicine for more than 2000 years, mainly for the treatment of jaundice, diseases of the liver, gallbladder (GB), spleen, constipation, hemorrhoids. The overwhelming part of the active ingredients of milk thistle is contained in its fruits, which received the effective name "the fruits of St. Mary". These active substances are 1–3% composed of flavonol derivatives. A mixture of the three major isomers of flavonoids is combined with the term "silymarin". The most potent of these flavonoids is silibinin [12]. In addition to flavonoids, thistle fruits contain 0.08% essential oil, tar, biogenic amines (tyramine, histamine), mucus, 16–18% fatty oil [3, 16].

The pharmacokinetics of silibinin has a number of features. It is well absorbed when taken per os, and the maximum concentration in the blood is reached in the next 30–60 minutes. At the same time, silibinin has a short half-life of slightly more than 6 hours, and it is completely removed within 72 hours, which indicates the absence of cumulative properties. Silibinin is distributed unevenly in the human body: it accumulates in the liver and kidneys, while its content in other organs is much less [25].

Scientific data accumulated up to the present, allow us to understand the mechanisms of action through which silibinin realizes its effects, interacting with various tissues. In this aspect, the action of silibinin is manifested by the modulation of the inflammatory process and apoptosis, which, together with antioxidant properties, are the key points that led to its use in the most diverse pathologies [49]. Silibinin acts by "turning off" pro-inflammatory signals resulting from the activation of the nuclear factor κB (NF-κB), involved in the induction of the synthesis of such cytokines as tumor necrosis factor-α (TNF-α), interleukin (IL) -1, IL- 6 and granulocyte-monocytic colony-stimulating factor. In addition, silibinin induces apoptosis by modulating the cytoplasmic level of bcl-2-like protein 4 (Bax) and B-cell lymphoma proteins, releasing cytochrome C and activating caspase-3, -9. Antioxidant properties are due to its ability to interact with free radical scavengers and lipid peroxidation inhibitors, as has been proven in vitro and in vivo [49].

Silymarin is also a estrogen signaling modulator, insulin sensitizer, a regulator of intracellular drug transport, an anticarcinogen, antidiabetic (due to the regulation of signals from receptors activated by the peroxisome-proliferator-γ; PPAR-γ), antifibrotic and choleretic agent (Fig. 2).

Flavonoids are active complexing agents. They form complex compounds and are involved in the elimination of heavy metal ions, radionuclides, and metals with variable valence, which activate lipid peroxidation [4, 5, 6]. Participating in the complexation of proteins and enzymes, silibinin plays a role in important enzymatic reactions, including in respiratory and oxidative phosphorylation. The detoxification properties of silibinin are also explained by the fact that it enters into competitive relations with hepatotropic poisons for its association with hepatocyte receptors [25].

The variety of mechanisms of action characteristic of silymarin explains the reason why many studies have been conducted that studied its effectiveness in various pathologies. In rheumatological diseases such as rheumatoid arthritis, silymarin acts as an anti-inflammatory agent by inhibiting the migration and activation of neutrophils in the joints. In various oncologic diseases, such as prostate cancer, vaginal cancer, hepatocellular carcinoma (HCC), cancer of the glands and lungs, silymarin reduces the viability and replication of metastatic cells [49].


**Рис. 2. Разнообразные терапевтические свойства силимарина (по A. Federico и соавт. (2017)) [55].**
Примечания. ИЛ-1/6: интерлейкин 1/6; ФНО-α: фактор некроза опухоли-α; ИФН-γ: - интерферон-γ; ГМКСФ - гранулацитарно-макроцитарно колониестимулирующий фактор; МАРК: митоген-активируемая протеинкиназа; Bax: bcl-2 подобный протеин; Bcl-2: В-клеточная лимфома 2; ИПФР: - инсулиноподобный фактор роста; ТФР-β: трансформирующий фактор роста-β; Akt: протеин-киназа В; GLUT4: транспортер глюкозы 4 типа.

Due to its detoxification properties, water-soluble intravenous silymarin is used as a hepatoprotective drug for poisoning with acetomenophene, arsenic, carbon tetrachloride, butyrophenone, phenothiazides and toxins of the pale toadstool. In hypercholesterolemia, silymarin/silibinin inhibits 3-hydroxy-3-methylglutaryl-coenzyme A (HMC-CoA) reductase, thereby reducing cholesterol (CH) synthesis. Finally, in neurological and psychiatric diseases, this molecule acts by "turning off" the inflammatory signals that underlie the degeneration of dopaminergic neurons in Parkinson's disease; Silymarin reduces the clinical symptoms associated with obsessive-compulsive disorder [49]. It should be noted that the effect of soluble herbal medicines on the course of chronic liver diseases (currently representing one of the pressing health problems in ≈10% of the world's population) is the most studied topic in the scientific community. The action of silymarin in chronic liver diseases is realized through various mechanisms and complex biological interactions, which can have a beneficial effect in various diseases, some of which are characterized by systemic damage with liver damage. For a long time, scientists have studied the biological effects of a natural compound such as silymarin in the pathogenesis of viral hepatitis, alcoholic liver disease, metabolic hepatitis, as well as such typical terminal hepatopathy as cirrhosis and HCC, in which silymarin has a significant biological effect.

The clinical efficacy of preparations containing silibinin has been proven in acute and chronic hepatitis viral, toxic etiology. Thus, in case of acute viral hepatitis, silibinin treatment reduces the time required to reduce by 50% the total and direct bilirubin content in the blood, the activity of alkaline phosphatase, and other blood enzymes. Silibinin is effective in toxic liver damage in cases of poisoning with pale toadstool, tetracycline, etc. In chronic hepatitis and liver cirrhosis (LC), silibinin helps reduce the severity of clinical manifestations (pain and heaviness in the right hypochondrium, dyspepsia) and activity of the process (decrease transaminases); improvement of protein synthesis and detoxification of the liver (elimination of dysproteinemia, normalization of indicators of the bromosulfalein test); correction of serum immunoglobulin levels [13, 25]. In patients with LC, long-term administration of silymarin (for 41 months), 0.14 g 3 times a day increased the survival rate of patients to 58±9% (in the control group 39±9%). Moreover, the best effect was obtained with alcohol-induced LC [25]. Silibinin is also indicated for alcoholic steatosis and hepatitis. By the end of the three-month treatment of patients with alcoholic liver steatosis, despite their continued intake of alcoholic beverages, under the influence of silibinin, 0.2 g three times a day decreases the activity of aminotransferases, alkaline phosphatase in the blood serum, the content of cholesterol and uric acid in the blood decreases, the indicators improve bromphenol test. Liver biopsy shows a significant decrease in fat content, sometimes by 50–75% [25, 44].

Silibinin is also highly effective in cases of fatty liver dystrophy of non-alcoholic etiology, for example, arising from exposure to hepatotoxic drugs. At the same time, within 7 days, the activity of glutamate pyruvattransaminase in patients with fatty liver or drug-induced hepatitis treated with silibinin is normalized, whereas in patients receiving placebo, this result occurs on day 23. Glutamate oxalate transaminase is normalized, respectively, at 10 and 14 days [25].

Silibinin preparations rarely cause dyspepsia, dry mouth, pruritus. Silibinin is undesirable in patients with a combination of diabetes mellitus (DM) and cholestasis [35].

Thus, silymarin has three important properties: anti-inflammatory, antioxidant, and proapoptotic, together they represent a “functional triad” that allows you to counteract the onset and progression of the damage mechanisms responsible for the progression of hepatitis and its transformation into LC and HCC [49]. It has been proven that in the terminal stages of liver disease, silymarin may limit de-novo fibrogenesis and interfere with the procarcinogenic mechanisms that cause HCC [49].

***Artichoke (Cynara scolymus L.)***

The second component of Engilen is the artichoke leaf extract (Cynara scolymus L.). It has been established that artichoke extract has choleretic properties, affects the tone and contractile

function of GB, and also has a hepatoprotective effect due to a pronounced antioxidant and hypocholesterolemic action [62]. Artichoke has antimicrobial properties against various types of pathogenic bacteria, yeast sticks and fungal flora [78, 79]. The positive effects of artichoke are probably the result of a high content of polyphenolic antioxidants [75]. Artichoke extract is more distinct than ascorbic acid, protects the endothelium from oxidative stress and has the ability to increase the secretion of nitric oxide [50, 54]. The antioxidant effect of artichoke leads to inhibition of the oxidation of low-density lipoproteins by increasing the activity of glutathione peroxidase [7, 53].

In addition to antioxidant, artichoke has a number of other healing properties. For example, artichoke extract inhibits gelatinase activity and the secretion of matrix metalloproteinase-9, protecting connective tissue from degradation [7, 43].

Artichoke extracts stimulate apoptosis of liver cancer cells through the mitochondrial-caspase mechanism [7, 62, 66]. Artichoke extracts are rich in minerals and trace elements: primarily calcium, potassium, magnesium and iron. Useful in practice in patients with comorbidity is the diuretic effect of artichoke.

Another component of the artichoke, inulin, has a significant therapeutic effect. Inulin is a polysaccharide found in tubers and roots of dahlias, artichokes and dandelions. It is a fructosan, since its hydrolysis produces fructose. It was shown that inulin, in addition to stimulating the growth and activity of bifidobacteria and lactobacilli, increases calcium absorption in the colon, i.e. reduces the risk of osteoporosis, affects lipid metabolism, reducing the risk of atherosclerotic vascular changes and, possibly, preventing the development of type 2 diabetes [18, 71]. There are preliminary data on the anticarcinogenic effect of inulin [59]. Inulin is easily absorbed by the human body, and therefore is also used as a substitute for starch and glucose in diabetes.

The artichoke contains a range of bioflavonoids with pronounced antioxidant properties (Fig. 3).

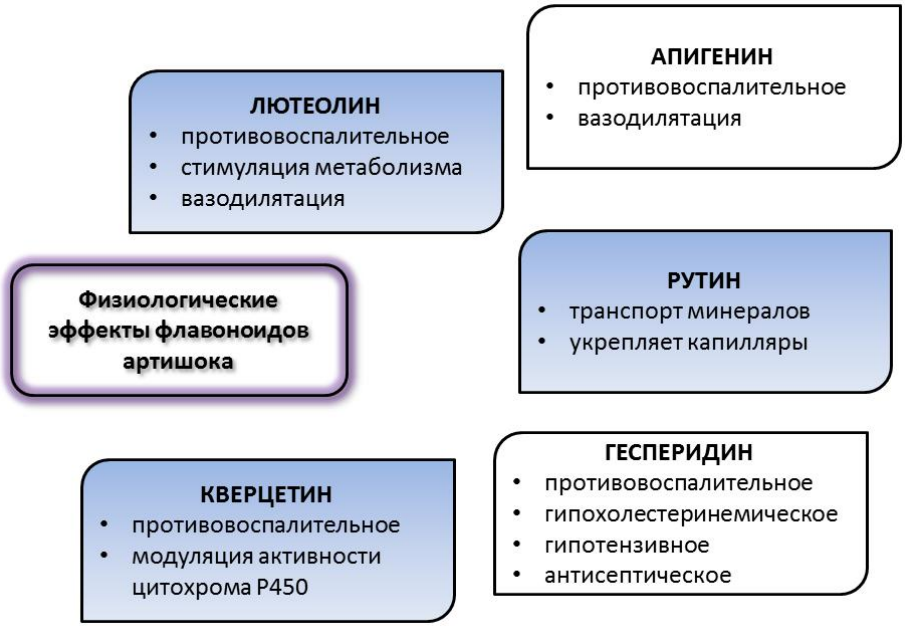


**Fig. 3. Physiological effects of artichoke flavonoids (O. A. Gromova et al., 2009 [7]).**

It is known that luteolin and apigenin are antioxidants isolated from artichokes. Apigenin is an antioxidant with anti-inflammatory and anti-tumor properties that can block the formation of uric acid. Luteolin and apigenin inhibit the production and secretion of proinflammatory cytokines: TNF-α and IL-1β, 4, 6, 13 [51]. Apigenin reduces the expression of genes of vascular epithelium growth factor and the factor induced by hypoxia [7, 48].

Other bioflavonoids have been found in artichoke extracts: hesperidin, quercetin and rutin.

Hesperidin is an antioxidant of the class of flavanones, it reduces the content of total cholesterol [63, 67], blood pressure, and also has antiseptic and anti-inflammatory effects [47]. Quercetin is the most active flavonoid antioxidant. Its anti-inflammatory effect consists in slowing down the synthesis and secretion of histamine, it is able to inhibit the enzyme lipoxygenase. Quercetin is a potent inhibitor of cytochrome CYP3A4, which is involved in the metabolism of drugs. Thus, quercetin can potentiate higher plasma levels of these drugs [7].

A systematic review and meta-analysis of 39 studies analyzing the effect of artichoke on the state of the liver has been published relatively recently [73]. It should be noted that of the trials included in the meta-analysis, 2 studies were conducted with the participation of people, 23 — with the involvement of laboratory animals, and 14 studies were carried out in vitro. After analyzing data from in vitro studies, the authors of the meta-analysis proved that the artichoke has an antioxidant effect. Having studied the results of experimental work, S. Salekzamani et al. (2019) confirmed that artichoke leaf extract increases the content of superoxide dismutase, catalase, glutathione in the liver, and also reduces the concentration of malondialdehyde in the liver and in the plasma of laboratory animals compared with placebo [73].

The effectiveness of artichoke in the treatment of various liver diseases has been proven not only in experimental but also in clinical studies. Y. Panahi and colleagues (2018), authors of a randomized double-blind study, recommended non-alcoholic fatty liver disease patients to take artichoke leaf extract at a dose of 600 mg/day (n = 49) or placebo (n = 41) for two months [69]. Researchers found that artichoke intake was accompanied by an improvement in blood flow through the hepatic vein ($p<0.001$), a decrease in portal vein diameter and liver size (in all cases $p <0.001$), a decrease in the ALT and AST levels, and a normal AST/ALT ratio <0.001), as well as a decrease in the level of total bilirubin compared with placebo. In addition, the use of artichoke leaf extract had a beneficial effect on the level of total cholesterol, cholesterol of low and high density lipoproteins, triglycerides ($p = 0.01$) compared with placebo.

The pronounced anti-inflammatory, antioxidant properties of the artichoke extract allow its wide use in the treatment of various diseases accompanied by the activation of inflammation and lipid peroxidation.

***Turmeric (Curcuma longa)***

The third component of Engilen — extract of turmeric rhizome long (Curcuma longa L.). For hundreds of years, curcumin, one of the components of this rhizome, has been known as an oriental (Indian) spice and has been used in cooking. Somewhat later began to use the therapeutic properties of turmeric: choleretic, anti-inflammatory, antioxidant.

Curcumin (diferuloylmethane) is a substance colored in yellow. Curcumin's high lipophilicity allows it to be rapidly absorbed in the digestive tract through passive diffusion. Currently, the “new” properties of curcumin have been discovered and studied: its ability to regulate the activity of various transcription factors, cytokines, protein kinases, adhesion molecules, redox states and enzymes associated with the immuno-inflammatory response.

Curcumin is a blocker (suppressor) of NF-κB-activation induced by many pro-inflammatory agents due to the inhibition of the IκB-α-kinase complex and Akt [41, 55, 74], which suppresses NF-κB-regulated gene products, apoptosis; He participates in the processes of proliferation and angiogenesis. Inhibition of the activation of curcumin NF-κB in tumor cells was observed, which was accompanied by suppression of anti-apoptotic proteins [15, 56].

Curcumin is used in the treatment of a wide range of diseases, the pathogenesis of which involves an immune inflammatory response, as well as in Alzheimer's and Parkinson's diseases, multiple sclerosis, epilepsy, cerebral palsy, cardiovascular diseases, rheumatoid arthritis, diabetes, depression and other diseases (Fig. 4) [1, 39, 77].


**Fig. 4. The therapeutic potential of curcumin in various diseases (B. B. Aggarwal et al., 2009 [40]).**

The in vitro antimicrobial activity of alcohol extract of turmeric, curcumin and its essential oils relative to gram-positive bacteria has been proven [60]. Curcumin has been shown to exhibit bactericidal and bacteriostatic properties against Staphylococcus aureus, Salmonella paratyphi, Mycobacterium tuberculosis. The experiment documented the antifungal and antiparasitic effects of curcumin. An important property of curcumin is inhibition of the end of the replication of the genome of the HIV-1 virus, without causing significant damage to the cells [58].

3 hours after administration of the aqueous and methanol extracts of turmeric, gastric secretion is suppressed; aqueous extract reduces acid secretion, while methanol extract mainly reduces pepsin secretion [72]. A. Munzenmaier et al. (1997) found that curcumin inhibits the synthesis of IL-8 induced by Helicobacter pylori [64]. Curcumin also inhibits the proliferation of gastric and rectal tumor cells [61].

Active ingredients of turmeric have antioxidant properties, improve abdominal digestion, because they stimulate gastric and pancreatic secretion [12]. In addition, phenipentol is involved in the activation of pancreatic lipase, improves emulsification of fats and their hydrolysis in the small intestine, increases the level of secretin in the blood, increasing the volume of pancreatic juice and the content of bicarbonates in it [35].

The hypocholesterolemic and hypolipidemic activity of curcumin has been demonstrated [52]. U.R. Deshpande et al. (1997) observed a significant decrease in triglycerides and a slightly less pronounced decrease in total blood cholesterol in the appointment of curcumin. The lipid-lowering effect was accompanied by a decrease in plasma lipid peroxidation [46]. These effects are particularly useful in the treatment of non-alcoholic fatty liver disease, lipid distress syndrome (see below).

One of the main properties of extracts of turmeric and curcumin is a hepatoprotective effect,

protecting the liver from the toxic effects of various substances. The positive effects of curcumin were found in experimental and clinical studies on viral hepatitis B and C, alcoholic liver disease, non-alcoholic fatty liver disease, primary biliary LC and primary sclerosing cholangitis, and medicinal liver damage [65, 70]. Many studies have confirmed choleretic and cholekinetic properties of curcumin, its ability to reduce the lithogenicity of bile. This is justified by the property of phenypentol to increase the content of bile acids in bile, while not significantly affecting the level of cholesterol in it, which helps to reduce the lithogenicity of bile [12, 13]. The choleretic effect of turmeric is dose-dependent: small doses increase the volume of the liquid part of bile, with increasing doses, the excretion of bilirubin increases [57, 61, 65].

A recently completed randomized controlled trial involving non-alcoholic fatty liver disease (n = 102) confirmed the effectiveness of curcumin in the treatment of this pathology [68]. Y. Panahi and colleagues (2017) divided NAFLD patients into two groups, recommending that patients of the main group take 1000 mg of curcumin per day, while those included in the comparison group received a placebo. After 8 weeks of treatment, the researchers analyzed the anthropometric, biochemical, and ultrasonographic characteristics. It turned out that taking curcumin was associated with a decrease in body mass index ($p = 0.003$), a decrease in waist volume ($p = 0.024$) compared with placebo. Curcumin had a beneficial effect on the activity of liver enzymes: in the main group, the level of ALT and AST decreased ($p < 0.001$), whereas in the control group, these indicators increased. In 70% of the participants in the main group, the researchers stated an improvement in the ultrasonographic state of the liver ($p < 0.001$); similar positive dynamics in the placebo group occurred in just 4.7% of patients. In conclusion, the authors of the study emphasized the high safety profile and good tolerability of curcumin.

**Engilen: features of clinical use**

Having examined the pharmacological properties of the components of the Engilen, we turn to the official indications for the appointment of the drug. Engilen is recommended as a dietary supplement to the diet as an additional source of silymarin, curcumin, tsinarina, flavonoids, chlorogenic and caffeic acids to normalize the functional state of the digestive system in dyspepsia, chronic hepatitis of various etiologies, toxic liver damage (including alcohol ) postcholecystectomy syndrome.

Adverse reactions in the treatment of Engilen rarely develop, in particular, with individual hypersensitivity to the components. The drug is contraindicated in obstructive jaundice, acute diseases of the liver, kidneys, bile and urinary tract, during pregnancy and lactation [29].

Despite the wide choice of phytohepatoprotectors in the pharmaceutical market of Ukraine, Engilen has certain advantages.

The most important advantage of Engilen is a logical and expedient combination of components that potentiate and complement each other's actions (Table 1).

*Table 1*

**Properties of the active ingredients of the drug Engilen**

| Properties | Holy thistle | Artichoke | Turmeric |
|---|---|---|---|
| Reduction of cholesterol and increasing the level of bile acids in bile | + | + | + |
| Choleretic effect | | + | + |
| Antispasmodic action | | | + |
| Antimicrobial effect | | | + |
| Anti-inflammatory effect | + | | + |
| Reduction of dyspeptic phenomena | | + | + |
| Analgesic effect | | | + |

| | | | |
|---|---|---|---|
| Stimulation of gastric and pancreatic secretion | | + | + |
| Reduction of fatty degeneration of the liver and pancreas | + | + | |
| Reduced blood cholesterol | + | + | + |
| Antioxidant properties | + | + | + |
| Antiatherogenic effect | + | + | + |
| Anti-inflammatory effect | + | | + |
| Hepatoprotector | + | + | |
| Immunomodulatory properties | | + | + |
| Efficacy in case of concomitant diseases (diuretic, etc.) | | + | + |

Thus, the combination of the main effects of silymarin (hepatoprotective, metabolic, antioxidant, detoxification), cinarin (hypolipidemic) and phenipentol (choleretic) substantiates the expediency of administering Engilen in chronic hepatitis, LC (both alcoholic, drug, as an auxiliary agent, and viral etiology ), with cholecystitis, cholangitis, various functional disorders of the motility of the biliary tract (dysfunction of the left ventricle and sphincter of Oddi), gastroduodenal zone (functional dyspepsia). In addition, Engilen can be prescribed as a symptomatic remedy to reduce the dyspeptic phenomena associated with other diseases of the digestive system.

The next advantage of Engilen is its pathogenetic and symptomatic action not only on the underlying disease of the digestive organs, which the patient suffers, but also on the concomitant, both gastroenterological and pathology of other organs and systems. This is important, because in the vast majority of patients in gastroenterological clinics, not one, but several diseases are diagnosed, especially in the older age groups. Thus, 70–90% of patients aged 40–60 years have an average of 4.8 simultaneously occurring diseases [32, 35].

In this regard, there are several examples. Thus, the combination of properties of turmeric cholepoiesis increase the content of bile acids in bile and its bactericidal properties and its ability to stimulate pancreatic secretion antioxidant qualities makes silibinin Engilen appropriate in biliary pancreatitis, developed due to cholecystitis, biliary sludge flowing and easy to exocrine pancreatic insufficiency.

The effectiveness of silibinin in fatty liver, its ability to detoxify acetaldehyde in combination with the property of curcumin to activate lipase, to improve emulsification of fats justify the administration of Engilen with combinations of alcoholic lesions of the liver and pancreas.

In chronic diffuse diseases of the liver, the intestinal flora is disturbed for the second time, a syndrome of excessive bacterial growth develops, which can serve as a resolving factor in relation to the development or exacerbation of hepatic encephalopathy. Turmeric's antimicrobial abilities are important for treating such patients.

Considering the literature data on the antifibrotic action of silibinin and on the increase in the life expectancy of patients with LC when it is taken for a long time (see above), the combination of silibinin with turmeric seems to be successful. In this regard, the antitumor properties of turmeric, which hypothetically may be important in reducing the likelihood of developing HCC in patients with LC (especially in viral etiology of the disease in the absence of antiviral therapy), are important [33]. In addition, based on the lipid-lowering properties, the artichoke in the composition of Engilen is useful in treating patients not only with chronic cholecystitis, but it seems promising to study the effectiveness of Engilen and in cholesterosis cholesterol.

If the patient has circulatory failure, pyelonephritis, cystitis, then the diuretic effect of the artichoke becomes appropriate (of course, Angilen has only auxiliary value in cardiovascular diseases, kidney disease).

The same diuretic effect of the artichoke justifies the use of Engilen in LC with portal hypertension if the patient with liver disease and biliary tract has a concomitant pathology of the

kidneys.

Vitamins A, C, which are components of plants belonging to the Engilen, also give the drug adaptogenic, nonspecific immunostimulating properties. At the same time, the majority of patients with diseases of the digestive organs have hypovitaminosis and secondary immunodeficiency [32, 34, 35, 36].

Thus, the use of the combined phytohepatoprotector Engilen is pathogenetically substantiated and indicated in chronic hepatitis, fatty liver, LC mostly of toxic etiology, in chronic cholecystitis, in dysfunction of the gastrointestinal tract, in Oddi's sphincter, and in if patients have a gastroenterological profile of concomitant diseases of the cardiovascular, urinary systems.

**Own experience of using Engilen**

*Aim of study*: evaluate the effectiveness of Engilen in the treatment of chronic pancreatitis and non-alcoholic steatohepatitis in patients with overweight and obesity.

*Materials and methods*. 32 patients with chronic cholecystitis with cholecystitis in the acute stage against non-alcoholic steatohepatitis with minimal biochemical activity and overweight or first degree obesity were examined. The diagnosis was made on the basis of the clinic, the results of biochemical, ultrasound and anthropometric studies. The dynamics of the activity of ALT, AST, and the level of total blood cholesterol were assessed. Ultrasound of the liver and GB in the dynamics of treatment was performed.

In addition, they conducted a dynamic sonography of the GB before and after the treatment. Variant dysfunction variant was assessed by its volume 15 and 60 minutes after the food load (2 yolks) relative to the fasting volume. The normal contractile function of GB and 4 variants of its dysfunction were distinguished: hyperkinetic-hypotonic, hyperkinetic-hypertonic, hypokinetic-hypotonic and hypokinetic-hypertonic. The reservoir function of gallstones was assessed by its volume on an empty stomach [2]. The results of the dynamic sonography of the GB are presented in Table 2

*Table 2*

**The volume of gall bladder and contractility index in the examined patients and healthy**

| Time of study | Patients n = 32 | Healthy n = 30 |
|---|---|---|
| GB volume on an empty stomach, ml | 108,7±3,8* | 85,3±2,2 |
| GB volume 15 min after load, ml | 36,3±2,8* | 60,4±2,4 |
| GB volume 60 min after load, ml | 63,4±2,2* | 48,4±3,2 |
| Contractility index | 2,99±0,08* | 1,82±0,04 |

Note: * — the difference between patients and healthy is significant ($p<0,05$).

Patients received recommendations for optimizing motor activity and nutrition, if necessary antispasmodics. All patients were prescribed Engilen 1 capsule in the morning and in the evening before meals, drinking water, for 18–20 days.

*Results.* All patients showed positive dynamics of clinical manifestations: pain and dyspeptic syndromes disappeared completely in 24 (75.0%) patients and significantly decreased in 8 (25.0%) patients. The treatment significantly reduced the activity of liver enzymes (ALT from 57.3±2.0 U/l to 31.6±1.8 U/l, while the standard — to 26.5±2.1 U/l; AST from 49, 7±2.1 U/l to 27.3±1.8 U/l at a rate of 24.4±1.9 U/l, as well as total cholesterol (with 10.8±0.6 mmol/l to 6.5±0.7 mmol/l at a rate of 5.4±1.6 mmol/l; in all cases $p<0.05$) (Fig. 5).

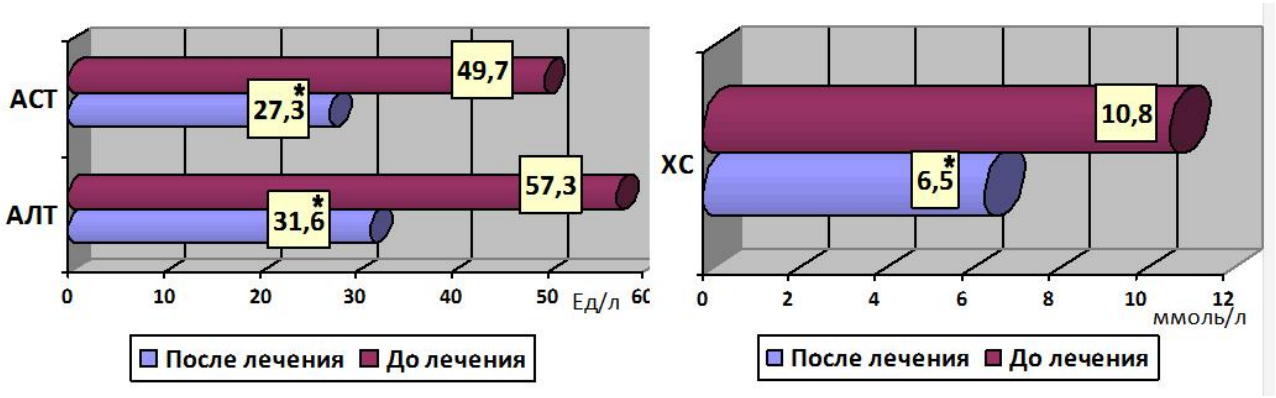


**Fig. 5. Levels of ALT, AST, total cholesterol in the dynamics of treatment with Engilen.**
Note: * — significant differences in treatment dynamics (p<0,05).

Before treatment, the volume of GB on an empty stomach, according to the data of dynamic sonography, was significantly increased in our patients, which reflects the presence of hypotonic dysfunction in them (Table 2). After treatment, the volume of GB on an empty stomach in patients decreased to 94.9±3.9 ml, however, this was only an unreliable orientation towards a change in the index (p> 0.05). The contractility index of GB after treatment significantly decreased to 2.43±0.09 (p <0.05). Thus, the inclusion of Engilen in the complex therapy of chronic calculous cholecystitis in combination with overweight and obesity effectively eliminates the hyperkinetic component of GB dysfunction (Fig. 6).

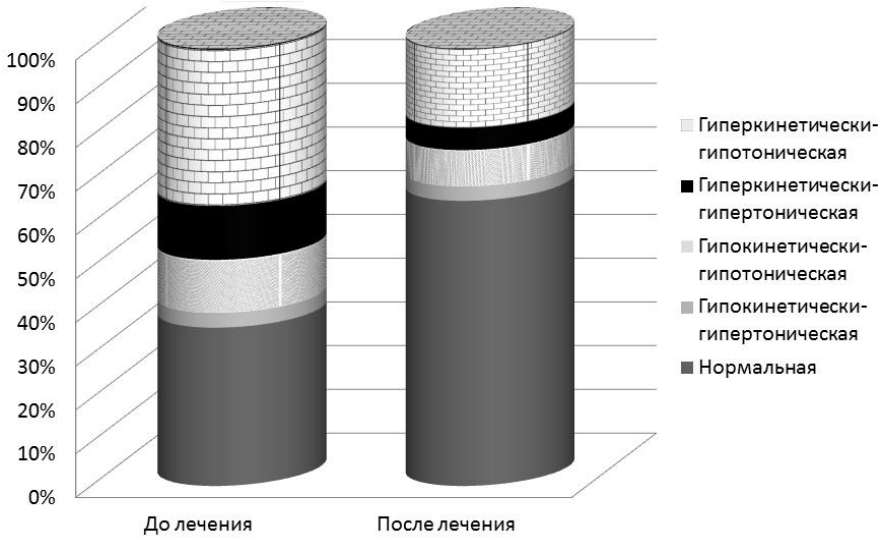


**Fig. 6. Frequency of detection of various GB dysfunctions in the examined patients.**

After treatment, the frequency of hyperkinetic-hypotonic and hyperkinetic-hypertonic variants of dysfunction of the GB was significantly less than before the treatment. For example, the frequency of hyperkinetic-hypotonic dysfunction in patients after treatment was 1.99 times less than before treatment, and the frequency of hyperkinetic-hypertonic dysfunction of GB was 2.42 times less than in the first study. Somewhat less after treatment than before treatment was hypokinetic-hypotonic GB dysfunction — 1.46 times. As a result of more effective elimination of inflammation of the mucous membrane of the GB and correction of its reservoir and contractile functions, normalization of the functional state of the organ by the end of therapy occurred in 62.5% of cases (in 20 patients).

We did not observe any adverse reactions in the examined patients.

In conclusion, we cite the statement of the distinguished physician G. A. Ilizarov: “We must be apprentices of nature” [22]. It is such drugs as Engilen that allow us to fully follow this advice.

Summarizing all the above, we can draw the following *conclusions*:

1. Engilen is a combined FitoGP with a rational and balanced composition and choleretic action.
2. Engilen is effective in the treatment of chronic cholecystitis without stones and non-alcoholic steatohepatitis in overweight and obese patients.
3. Engilen contributes to the correction of gallbladder dysfunction in patients with combined pathology.

Prospects for further research are, in our opinion, in the study of the therapeutic potential of Engilen in other chronic diffuse diseases of the liver (alcohol, drugs, etc.), GB cholesterosis, biliary sludge.

**References:**


1. Бабак О. Я. Хронические гепатиты. Киев: Блиц–Информ, 1999. 208 с.
   [Babak O. Y. Khronicheskiye gepatity. Kyiv: Blits–Inform, 1999. 208 s.]
2. Бутов М. А., Ардатова В. Б., Шелухина С. В. Дисфункции билиарного тракта: диагностика, медикаментозная коррекция. Рязань, 2004. 39 с.
   [Butov M. A., Ardatova V. B., Shelukhina S. V. Disfunktsii biliarnogo trakta: diagnostika, medikamentoznaya korrektsiya. Ryazan', 2004. 39 s.]
3. Гаммерман А. Ф., Кадаев Г. Н., Шупинская М. Д., Яценко-Хмелевский А. А. Лекарственные растения. Москва: Высшая Школа, 1975. 389 с.
   [Gammerman A. F., Kadayev G. N., Shupinskaya M. D., Yatsenko-Khmelevskiy A. A. Lekarstvennyye rasteniya. Moskva: Vysshaya Shkola, 1975. 389 s.]
4. Гарник Т. Гепатопротекторное действие фитосредств в комплексной терапии и реабилитации больных хроническим гепатитом. *Ліки України*. 2002. № 11. С. 2–5.
   [Garnik T. Gepatoprotektornoye deystviye fitosredstv v kompleksnoy terapii i reabilitatsii bol'nykh khronicheskim gepatitom. *Liki Ukraini*. 2002. № 11. S. 2–5.]
5. Грек О. Р. Новые аспекты фармакологического действия оригинальных полифенольных комплексов, выделенных из растительной флоры Сибири и Алтайского края. *Введение в общую микронутриентологию*. Под ред. Ю. П. Гичева, Э. Огановой. Новосибирск, 1999. С. 111–150.
   [Grek O. R. Novyye aspekty farmakologicheskogo deystviya original'nykh polifenol'nykh kompleksov, vydelennykh iz rastitel'noy flory Sibiri i Altayskogo kraya. *Vvedeniye v obshchuyu mikronutriyentologiyu*. Pod red. Y. P. Gicheva, E. Oganovoy. Novosibirsk, 1999. S. 111–150.]
6. Грек О. Р. Растительные биофлавоноиды и их биологические и фармакологические свойства. *Введение в частную микронутриентологию*. Под ред. Ю. П. Гичева, Э. Огановой. Новосибирск, 1999. С. 219–239.
   [Grek O. R. Rastitel'nyye bioflavonoidy i ikh biologicheskiye i farmakologicheskiye svoystva. *Vvedeniye v chastnuyu mikronutriyentologiyu*. Pod red. Y. P. Gicheva, E. Oganovoy. Novosibirsk, 1999. S. 219–239.]
7. Громова О. А., Торшин И. Ю. Хофитол стандартизированный экстракт артишока. Биохимический состав и фармакологические эффекты. *Трудный пациент*. 2009. Т. 7, № 45. С. 24–31.
   [Gromova O. A., Torshin I. Yu. Khofitol standartizirovannyy ekstrakt artishoka. Biokhimicheskiy sostav i farmakologicheskiye effekty. *Trudnyy patsiyent*. 2009. T. 7, № 45. S. 24–31.]
8. Губергриц А. Я., Соломченко Н. И. Лекарственные растения Донбасса. Донецк: Донбасс, 1990. 280 с.
   [Gubergrits A. Y., Solomchenko N. I. Lekarstvennyye rasteniya Donbassa. Donetsk: Donbass, 1990. 280 s.]
9. Губергриц Н. Б., Фадеенко Г. Д., Лукашевич Г. М., Фоменко П. Г. Гепатопротекторы: от теории к практике. Донецк: Лебедь, 2012. 156 с.
   [Gubergrits N. B., Fadeyenko G. D., Lukashevich G. M., Fomenko P. G. Gepatoprotektory: ot

teorii k praktike. Donetsk: Lebed', 2012. 156 s.]
10. Губергріц Н. Б., Харченко Н. В. Хронічні гепатити та цирози печінки. Київ: Поліум, 2015. 288 с.
[Huberhrits N. B., Kharchenko N. V. Khronichni hepatyty ta tsyrozy pechinky. Kyiv: Polium, 2015. 288 s.]
11. Дадали В. А. Процессы перекисного окисления в организме и природные антиоксиданты. *Введение в частную микронутриентологию*. Под ред. Ю. П. Гичева, Э. Огановой. Новосибирск, 1999. С. 240–263.
[Dadali V. A. Protsessy perekisnogo okisleniya v organizme i prirodnyye antioksidanty. *Vvedeniye v chastnuyu mikronutriyentologiyu*. Pod red. Y. P. Gicheva, E. Oganovoy. Novosibirsk, 1999. S. 240–263.]
12. Дегтярева И. И., Скрыпник И. Н., Невойт А. В. Гепатопротекторы-антиоксиданты в терапии больных с хроническими диффузными заболеваниями печени. *Новые мед. технологии*. 2002. № 6. С. 18–23.
[Degtyareva I. I., Skrypnik I. N., Nevoyt A. V. Gepatoprotektory-antioksidanty v terapii bol'nykh s khronicheskimi diffuznymi zabolevaniyami pecheni. *Novyye med. tekhnologii*. 2002. № 6. S. 18–23.]
13. Дегтярьова І. І., Осьодло Г. В., Скрипник І. М. Застосування силімаріновмісних препаратів для лікування хронічних токсичних гепатитів і жирової дистрофії печінки. *Здоров'я України*. 2001. № 10. С. 14.
[Dehtyar′ova I. I., Os′odlo H. V., Skrypnyk I. M. Zastosuvannya sylimarinovmisnykh preparativ dlya likuvannya khronichnykh toksychnykh hepatytiv i zhyrovoyi dystrofiyi pechinky. *Zdorov'ya Ukrayiny*. 2001. № 10. S. 14.]
14. Диагностика и лечение хронических гепатитов. *Лікування та діагност*. 1999. № 1. С. 9–13.
[Diagnostika i lecheniye khronicheskikh gepatitov. *Likuvannya ta diagnost*. 1999. № 1. S. 9–13.]
15. Залесский В. Н. Дисрегуляция иммуновоспалительного ответа ключевой фактор развития хронических (неинфекционных) заболеваний человека. Терапевтический потенциал куркумина. *Укр. мед. часопис*. 2011. № 1. С. 81–88.
[Zalesskiy V. N. Disregulyatsiya immunovospalitel'nogo otveta klyuchevoy faktor razvitiya khronicheskikh (neinfektsionnykh) zabolevaniy cheloveka. Terapevticheskiy potentsial kurkumina. *Ukr. med. chasopis*. 2011. № 1. S. 81–88.]
16. Йорданов Д., Николов П., Бойчинов А. Физиотерапия. София: Медицина и физкультура, 1968. 323 с.
[Iordanov D., Nikolov P., Boychinov A. Fizioterapiya. Sofiya: Meditsina i fizkul'tura, 1968. 323 s.]
17. Катикова О. Ю., Костин Я. В., Тишки В. С. Гепатопротекторное действие препаратов растительного происхождения. *Эксперим. и клин. фармакол*. 2002. № 1. С. 41–43.
[Katikova O. Y., Kostin YA. V., Tishki V. S. Gepatoprotektornoye deystviye preparatov rastitel'nogo proiskhozhdeniya. *Eksperim. i klin. farmakol*. 2002. № 1. S. 41–43.]
18. Каширская Н. Ю. Значение пробиотиков и пребиотиков в регуляции кишечной микрофлоры. *Рус. мед. журн*. 2000. № 13–14. С. 572–576.
[Kashirskaya N. Y. Znacheniye probiotikov i prebiotikov v regulyatsii kishechnoy mikroflory. Rus. med. zhurn. 2000. № 13–14. S. 572–576.]
19. МОЗ України, Укр. центр наук.-метод. інформ. та патент.-ліценз. роботи. Застосування легалону для лікування хронічних токсичних гепатитів і жирової дистрофії печінки: метод. рекомендації. Київ, 2002. 8 с.
[MOZ Ukrayiny, Ukr. tsentr nauk.-metod. inform. ta patent.-litsenz. roboty. Zastosuvannya lehalonu dlya likuvannya khronichnykh toksychnykh hepatytiv i zhyrovoyi dystrofiyi pechinky: metod. rekomendatsiyi. Kyiv, 2002. 8 s.]
20. МОЗ України, Укр. центр наук.-метод. інформ. та патент.-ліценз. роботи. Сучасна

фармакотерапія захворювань жовчного міхура та жовчовивідних шляхів: метод. рекомендації. Харків, 2000. 32 с.
[MOZ Ukrayiny, Ukr. tsentr nauk.-metod. inform. ta patent.-litsenz. roboty. Suchasna farmakoterapiya zakhvoryuvan′ zhovchnoho mikhura ta zhovchovyvidnykh shlyakhiv: metod. rekomendatsiyi. Kharkiv, 2000. 32 s.]
21. МОЗ України, Укр. центр наук.-метод. інформ. та патент.-ліценз. роботи. Сучасна фармакотерапія хронічних гепатитів: метод. рекомендації. Харків, 1997. 16 с.
[MOZ Ukrayiny, Ukr. tsentr nauk.-metod. inform. ta patent.-litsenz. roboty. Suchasna farmakoterapiya khronichnykh hepatytiv: metod. rekomendatsiyi. Kharkiv, 1997. 16 s.]
22. Мудрые мысли о медицине и врачевании. Сост. Я. С. Циммерман. Москва: ГЭОТАР-Медиа, 2015. 256 с.
[Mudryye mysli o meditsine i vrachevanii. Sost. Ya. S. Tsimmerman. Moskva: GEOTAR-Media, 2015. 256 s.]
23. Препарати з гепатопротекторною дією, дозволені для застосування в Україні. *Лікування та діагност*. 1999. № 1. С. 14–15.
[Preparaty z hepatoprotektornoyu diyeyu, dozvoleni dlya zastosuvannya v Ukrayini. *Likuvannya ta diahnost*. 1999. № 1. S. 14–15.]
24. Рыжикова М. А., Фархутдинов Р. Р., Загидуллин Ш. З. Влияние лекарственных растений на процессы свободнорадикального окисления в модельных системах. *Здравоохр. Башкортостана*. 1998. № 5–6. С. 38–41.
[Ryzhikova M. A., Farkhutdinov R. R., Zagidullin SH. Z. Vliyaniye lekarstvennykh rasteniy na protsessy svobodnoradikal'nogo okisleniya v model'nykh sistemakh. *Zdravookhr. Bashkortostana*. 1998. № 5–6. S. 38–41.]
25. Скакун Н. П., Шманько В. В., Охримович Л. М. Клиническая фармакология гепатопротекторов. Тернополь: Збруч, 1995. 272 с.
[Skakun N. P., Shman'ko V. V., Okhrimovich L. M. Klinicheskaya farmakologiya gepatoprotektorov. Ternopol': Zbruch, 1995. 272 s.]
26. Соколов С. Я., Замотаев И. П. Справочник по лекарственным растениям. Москва: Медицина, 1984. 464 с.
[Sokolov S. Y., Zamotayev I. P. Spravochnik po lekarstvennym rasteniyam. Moskva: Meditsina, 1984. 464 s.]
27. Справочник Видаль. Москва: Видаль Рус, 2017. 1240 с.
[Spravochnik Vidal'. Moskva: Vidal' Rus, 2017. 1240 s.]
28. Сравнительная характеристика современных гепатопротекторов. *Доктор*. 2001. № 2. С. 43–47.
[Sravnitel'naya kharakteristika sovremennykh gepatoprotektorov. Doktor. 2001. № 2. S. 43–47.]
29. Степанов Ю. М., Кононов І. М. Застосування Енгілену при дискінезії жовчовивідних шляхів: інформаційний лист. Київ: Укрмедпатентінформ, 2016. 3 с.
[Stepanov Y. M., Kononov I. M. Zastosuvannya Enhilenu pry dyskineziyi zhovchovyvidnykh shlyakhiv: informatsiynyy lyst. Kyyiv: Ukrmedpatentinform, 2016. 3 s.]
30. Фархутдинов Р. Р., Загидуллин Ш. З., Абдрашитова Н. Ф. Биоантиоксиданты и проблемы их применения в клинической практике. *Здравоохр. Башкортостана*. 1996. № 1. С. 41–48.
[Farkhutdinov R. R., Zagidullin S. Z., Abdrashitova N. F. Bioantioksidanty i problemy ikh primeneniya v klinicheskoy praktike. *Zdravookhr. Bashkortostana*. 1996. № 1. S. 41–48.]
31. Фархутдинов Р. Р., Лиховских В. А. Хемилюминесцентные методы исследования свободнорадикального окисления в биологии и медицине. Уфа, 1995. 87 с.
[Farkhutdinov R. R., Likhovskikh V. A. Khemilyuminestsentnyye metody issledovaniya svobodnoradikal'nogo okisleniya v biologii i meditsine. Ufa, 1995. 87 s.]
32. Харченко Н. В. Гепатология: проблемы и поиски. Особенности течения заболеваний и оптимизация лечения. *Доктор*. 2001. № 2. С. 6–7.

[Kharchenko N. V. Gepatologiya: problemy i poiski. Osobennosti techeniya zabolevaniy i optimizatsiya lecheniya. *Doktor*. 2001. № 2. S. 6–7.]
33. Харченко Н. В. Порівняльна характеристика сучасних гепатопротекторів. *Вісник фармакології та фармації.* 2001. № 3–4. С. 18–25.
[Kharchenko N. V. Porivnyal′na kharakterystyka suchasnykh hepatoprotektoriv. *Visnyk farmakolohiyi ta farmatsiyi*. 2001. № 3–4. S. 18–25.]
34. Харченко Н. В., Черненко В. В., Родонежская Е. В. Постхолецистэктомический синдром или дисфункция сфинктера Одди? *Здоров'я України*. 2003. № 8. С. 32–33.
[Kharchenko N. V., Chernenko V. V., Rodonezhskaya Ye. V. Postkholetsistektomicheskiy sindrom ili disfunktsiya sfinktera Oddi? *Zdorov'ya Ukraini*. 2003. № 8. S. 32–33.]
35. Циммерман Я. С. Гастроэнтерология. Москва: ГЭОТАР-Медиа, 2015. 816 с.
[Tsimmerman Y. S. Gastroenterologiya. Moskva: GEOTAR-Media, 2015. 816 s.]
36. Циммерман Я. С. Хронический холецистит и хронический панкреатит. Пермь: Перм. гос. мед. академия, 2002. 252 с.
[Tsimmerman Y. S. Khronicheskiy kholetsistit i khronicheskiy pankreatit. Perm': Perm. gos. med. akademiya, 2002. 252 s.]
37. Чекман И. С., Липкан Г. Н. Растительные лекарственные средства. Киев: Колос, 1993. 384 с.
[Chekman I. S., Lipkan G. N. Rastitel'nyye lekarstvennyye sredstva. Kiyev: Kolos, 1993. 384 s.]
38. Aggarwal B. B., Harikumar K. B. Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. *Int. J. Biochem. Cell Biol*. 2009. Vol. 41, No 1. P. 40–59.
39. Aggarwal B. B., Krishnan S., Guha S. Inflammation, life style and chronic diseases: the silent link (oxidative stress and disease). Boca Raton: CRC Press, 2011. 480 p.
40. Aggarwal B. B., Sung B. Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets. *Trends Pharmacol. Sci.* 2009. Vol. 30, No 2. P. 85–94.
41. Aoki H., Takada Y., Kondo S. Evidence that curcumin suppresses the growth of malignant gliomas in vitro and in vivo through induction of autophagy: role of Akt and extracellular signal-regulated kinase signaling pathways. *Mol. Pharmacol*. 2007. Vol. 72, No 1. P. 29–39.
42. Ball S. S., Weindruch R., Walford R. I. Antioxidants and immune response. *Free Radic., Aging and Degenerative Diseases*. 1986. Vol. 5. P. 427–456.
43. Bellosta S., Bogani P., Canavesi M. Mediterranean diet and cardioprotection: wild artichoke inhibits metalloproteinase 9. *Mol. Nutr. Food Res*. 2008. Vol. 52, No 10. P. 1147–1152.
44. Carini F., Bartolucci E., Cristallini E. L'impiego della silimarina nel trittamento della steatosi epatica alcoolica. *Clin. Ter*. 1985. Vol. 114. P. 307–314.
45. Chang H., But P. P. Pharmacology and applications of chinese materia medica. Vol. 2. Singapore: World Scientific Publishing Company, 1987.
46. Deshpande U. R., Joseph L. J., Manjure S. S. Effects of turmeric extract on lipid profile in human subjects. *Med. Sci. Res*. 1997. Vol. 25. P. 695–698.
47. Emim J. A., Oliveira A. B., Lapa A. J. Pharmacological evaluation of the antiinflammatory activity of a citrus bioflavonoid, hesperidin, and the isoflavonoids, duartin and claussequinone, in rats and mice. *J. Pharm. Pharmacol*. 1994. Vol. 46, No 2. P. 118–122.
48. Fang J., Xia C., Cao Z. Apigenin inhibits VEGF and HIF1 expression via PI3K/AKT/p70S6K1 and HDM2/p53 pathways. *FASEB J*. 2005. Vol. 19, No 3. P. 342–353.
49. Federico A., Dallio M., Loguercio C. Silymarin/Silybin and Chronic Liver Disease: A Marriage of Many Years. *Molecules.* 2017. № 22(2). P: E191.
50. Grande S., Bogani P., de Saizieu A. Vasomodulating potential of mediterranean wild plant extracts. *J. Agric. Food Chem*. 2004. Vol. 52, No 16. P. 5021–5026.
51. Hirano T., Higa S., Arimitsu J. Flavonoids such as luteolin, fisetin and apigenin are inhibitors of interleukin4 and interleukin13 production by activated human basophils. *Int. Arch. Allergy*

*Immunol*. 2004. Vol. 134, No 2. P. 135–140.
52. Hussain M., Chandrasekhara N. Effects of curcumin of cholesterol gall-stone induction in mice. *Indian J. Med. Res*. 1992. Vol. 96. P. 288–291.
53. Jimenez-Escrig A., Dragsted L. O., Daneshvar B. In vitro antioxidant activities of edible artichoke (Cynara scolymus L.) and effect on biomarkers of antioxidants in rats. *J. Agric. Food Chem*. 2003. Vol. 51, No 18. P. 5540–5545.
54. Juzyszyn Z., Czerny B., Pawlik A., Drozdzik M. The effect of artichoke (Cynara scolymus L.) extract on ROS generation in HUVEC cells. *Phytother. Res*. 2008. Vol. 22, No 9. P. 1159–1161.
55. Kamat A. M., Sethi G., Aggarwal B. B. Curcumin potentiates the apoptotic effects of chemotherapeutic agents and cytokines through down-regulation of nuclear factor-kappaB and nuclear factor-kappaB-regulated gene products in IFN-alpha-sensitive and IFN-alpha-resistant human bladder cancer cells. *Mol. Cancer Ther*. 2007. Vol. 6, No 3. P. 1022–1030.
56. Kunnumakkara A. B., Guha S., Krishnan S. Curcumin potentiates antitumor activity of gemcitabine in an orthotopic model of pancreatic cancer through suppression of proliferation, angiogenesis, and inhibition of nuclear factor-kappaB-regulated gene products. *Cancer Res.* 2007. Vol. 67, No 8. P. 3853–3861.
57. Li Y., Li M., Wu S., Tian Y. Combination of curcumin and piperine prevents formation of gallstones in C57BL6 mice fed on lithogenic diet: whether NPC1L1/ SREBP2 participates in this process? *Lipids in Health and Disease*. 2015. Vol. 14, No 100. P. 1–8.
58. Li Z. J., Zhang L. J., Dezube D. J. Three inhibitors of type 1 human inimunodeficiency virus long terminal repeat-directed gene expression and virus replication. *Proc. Natl. Acad. Sci. USA*. 1993. Vol. 90. P. 1839–1842.
59. Loo V., Cummings J. A., Delzenne J. A. Functional food properties of non-digestible oligosaccharides: a consensus report from the ENDO project (DGXII AIRII-CT94-1095). *Br. J. Nutr*. 1999. Vol. 81, No 2. P. 121–132.
60. Lutomski J., Kedzia B., Debska W. Effect of an alcohol extract and of active ingredients from Curcuma longa on baceria and fungi. *Planta Med*. 1974. Vol. 26, No 1. P. 9–19.
61. Mesa M. D., Ramirez-Tortosa M. C., Aguilera C. M. Pharmacological and nutritional effects of Curcuma longa L. extracts and curcuminoids. *Ars Pharmaceutica*. 2000. Vol. 41, No 1. P. 307–321.
62. Miccadei S., Di Venere D., Cardinali A. Antioxidative and apoptotic properties of polyphenolic extracts from edible part of artichoke (Cynara scolymus L.) on cultured rat hepatocytes and on human hepatoma cells. *Nutr. Cancer*. 2008. Vol. 60, No 2. P. 276–283.
63. Monforte M. T., Trovato A., Kirjavainen S. Biological effects of hesperidin, a Citrus flavonoid (note II): hypolipidemic activity on experimental hypercholesterolemia in rat. *Farmaco*. 1995. Vol. 50, No 9. P. 595–599.
64. Munzenmaier A., Lange C., Glocker E. A secreted/shed product of Helicobacter pylori activates transcription factor nuclear factor-kappa B. *J. Immunol*. 1997. Vol. 159, No 12. P. 6140–6147.
65. Nabavi S. F., Daglia M., Moghaddam A. H. Curcumin and liver disease: from chemistry to medicine. *Comprehensive Reviews in Food Science and Food Safety*. 2014. Vol.13. P. 62–77.
66. Nadova S., Miadokova E., Mucaji P. Growth inhibitory effect of ethyl acetatesoluble fraction of Cynara cardunculus L. in leukemia cells involves cell cycle arrest, cytochrome c release and activation of caspases. *Phytother. Res*. 2008. Vol. 22, No 2. P. 165–168.
67. Ohtsuki K., Abe A., Mitsuzumi H. Glucosyl hesperidin improves serum cholesterol composition and inhibits hypertrophy in vasculature. *J. Nutr. Sci. Vitaminol*. 2003. Vol. 49, No 6. P. 447–450.
68. Panahi Y., Kianpour P, Mohtashami R, Jafari R, Simental-Mendía L. E. Efficacy and Safety of Phytosomal Curcumin in Non-Alcoholic Fatty Liver Disease: A Randomized Controlled Trial. *Drug Res (Stuttg).* 2017. Vol. 67 No 4. P. 244–251.
69. Panahi Y., Kianpour P., Mohtashami R., Atkin S. L. Efficacy of artichoke leaf extract in non-

alcoholic fatty liver disease: a pilot double-blind randomized controlled trial. *Phytother Res.* 2018. Vol. 32, No 7. P. 1382–1387.
70. Rivera-Espinoza Y., Muriel P. Pharmacological actions of curcumin in liver diseases or damage. *Liver International*. 2009. Vol. 29, No 10. P. 1457–1466.
71. Roberfroid M. B. Prebiotics and probiotics: are they functional foods? *Am. J. Clin. Nutr*. 2000. Vol. 76, No 6 (Suppl.). P. 1682–1687.
72. Sakai K., Miyazaki Y., Yamane T. Effect of extracts of Zingiberaceae herbs on gastric secretion in rabbits. *Chem. Pharm. Bull*. 1989. Vol. 37. P. 215–217.
73. Salekzamani S, Ebrahimi-Mameghani M, Rezazadeh K. The antioxidant activity of artichoke (Cynara scolymus): A systematic review and meta-analysis of animal studies. *Phytother Res.* 2019. Vol. 33, No 1. P. 55–71.
74. Shishodia S., Amin H. M., Lai R., Aggarwal B. B. Curcumin (diferuloylmethane) inhibits constitutive NF-kappaB activation, induces G1/S arrest, suppresses proliferation, and induces apoptosis in mantle cell lymphoma. *Biochem. Pharmacol*. 2005. Vol. 70, No 5. P. 700–713.
75. Skarpanska-Stejnborn A., Pilaczynska-Szczesniak L., Basta P. The influence of supplementation with artichoke (Cynara scolymus L.) extract on selected redox parameters in rowers. *Int. J. Sport Nutr. Exerc. Metab*. 2008. Vol. 18, No 3. P. 313–327.
76. Srinivas L., Shalini V. K., Shylaja M. Turmerin: a water soluble antioxidant peptide from turmeric (Curcuma longa). *Arch. Biochem. Biophys*. 1992. Vol. 292, No 2. P. 617–623.
77. Surh Y. J., Packer L. Oxidative stress, inflammation, and health. Boca Raton: CRC Press, 2005. 660 p.
78. Zhu X. F., Zhang H. X., Lo R. Antifungal activity of Cynara scolymus L. *Fitoterapia*. 2005. Vol. 76, No 1. P. 108–111.
79. Zhu X. F., Zhang H. X., Lo R. Phenolic compounds from the leaf extract of artichoke (Cynara scolymus L.) and their antimicrobial activities. *J. Agric. Food Chem*. 2004. Vol. 52, No 24. P. 7272–7278.

**Engilen: from different therapeutic possibilities to effective clinical use**

N. B. Gubergrits, N. V. Byelyayeva, A. Ye. Klochkov, P. G. Fomenko, G. M. Lukashevich
*Donetsk National Medical University (Lyman)*

**Key words:** phytohepatoprotectors, silymarin, inulin, curcumin, Engilen, chronic cholecystitis, non-alcoholic steatohepatitis, dysfunction of the gallbladder

Composition of the Engilen preparation, medicinal properties of plants that make up the preparation, indications for its prescription are analyzed in detail in the article. Particular attention is paid to the advantages of Engilen, such as: optimal doses and ratio of active ingredients, wide range of indications, effectiveness upon combined diseases of the digestive system and with the concomitant pathology of other organs and systems. The results of our own study are presented, showing the effectiveness of Engilen upon chronic acalculous cholecystitis and non-alcoholic steatohepatitis in patients with excessive body mass or obesity. In addition, an effective correction of various types of the gallbladder dysfunction has been obtained.