

REVIEW OF THE PHARMACOLOGICAL PROPERTIES OF HERBAL PREPARATIONS AS POTENTIAL INGREDIENTS OF COMBINED MEDICATION FOR HEPATOBILIARY DISORDERS TREATMENT AMONG SERVICEMEN

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Purpose. To study and analyse the results of pharmacological studies of herbal substances and their preparations with regards to hepatoprotective, hepatoregenerative, choleretic, and antispasmodic effects. To determine the conceptual composition of a combination of herbal medicinal products for use in the treatment of hepatobiliary system disorders in military personnel.

Materials and methods. The bibliosemantic method was used in conducting the research. The study materials included scientific publications in professional journals.

Results. The analysis of pharmacological and clinical studies of herbal preparations obtained from the Milk thistle (*Silybum marianum* (L.) Gaerth.), Artichoke (*Cynara scolymus* L.) and Peppermint (*Mentha piperita* L.) was conducted. It was established that the studied preparations exhibit characteristic hepatoprotective, choleretic, antispasmodic, hypolipidemic, and anti-inflammatory activity, which characterises these substances as promising components of a combination medicinal product for the treatment of liver and biliary tract disorders.

Conclusions. Based on the analysis results, it can be concluded that the use of combination plant-based medicinal products is promising for the treatment of hepatobiliary system disorders in military personnel. Such products possess a broad and predictable spectrum of pharmacological action and are safe for long-term use. The next stages of research should include the development of the composition and technology of the finished medication as well as its target quality profile.

Key words: plant raw materials, hepatoprotectors, preparation, technology, technological process, polyphenols, flavonoids.

ОГЛЯД ФАРМАКОЛОГІЧНИХ ВЛАСТИВОСТЕЙ РОСЛИННИХ ПРЕПАРТІВ ЯК ПОТЕНЦІЙНИХ ІНГРЕДІЄНТІВ КОМБІНОВАНОГО ЗАСОБУ ДЛЯ ЛІКУВАННЯ РОЗЛАДІВ ГЕПАТОБІЛІАРНОЇ СИСТЕМИ У ВІЙСЬКОВОСЛУЖБОВЦІВ

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Мета. Вивчити та проаналізувати результати фармакологічних досліджень рослинних об'єктів та їх препаратів, з огляду гепатопротекторної, гепаторегенеруючої, холеретичної, та спазмолітичної дії. Визначити концептуальний склад комбінації рослинного лікарського засобу для застосування в лікуванні розладів гепатобіліарної системи у військовослужбовців.

Матеріали і методи. При проведенні дослідження було використано бібліосемантичний метод. Матеріалами дослідження були наукові публікації в фахових виданнях.

Результати. Проведено аналіз фармакологічних та клінічних досліджень рослинних препаратів, одержаних з рослин Розторопши плямистої (*Silybum marianum* (L.) Gaerth.), Артишоку посівного (*Cynara scolymus* L.) та М'яти перцевої (*Mentha piperita* L.). Встановлено, що досліджувані препарати здатні проявляти характерну гепатопротекторну, холеретичну, спазмолітичну, гіполіпідемічну та протизапальну активність, що характеризує дані об'єкти як перспективні складові комбінованого лікарського засобу для лікування розладів печінки і жовчаних шляхів.

Висновки. За результатами проведеного аналізу, можна говорити про перспективність застосування комбінованих рослинних лікарських засобів в лікуванні розладів гепатобіліарної системи у військовослужбовців. Такі засоби володіють широким і прогнозованим спектром фармакологічної дії та є безпечними при довготривалому застосуванні. Наступними етапами досліджень мають стати розробка складу та технології готового лікарського засобу та його цільового профілю якості.

Ключові слова: рослинна сировина, гепатопротектори, препарат, технологія, технологічний процес, поліфенольні сполуки, флавоноїди.

Introduction. Digestive diseases are an annual cause of death for two million people and constitute 4% of global total mortality [24]. The digestive diseases, including those of the hepatobiliary system, rank fourth among the causes of mortality in Ukraine, behind only cardiovascular disease, neoplasm and external reasons. From individual nosologies, chronic diseases of the liver and cirrhosis have the highest share in the structure of mortality behind this grade of reasons. The standardized mortality rates of the population of Ukraine from chronic liver diseases and cirrhosis are significantly higher than those in the EU and countries of the WHO European region [1].

In addition to the general causes of liver diseases in military personnel, injuries can significantly affect the function and condition of the hepatobiliary system [3].

The survey results indicate that in 34.2% of military personnel who sustained combat injuries, elevated aminotransferase levels were observed from the first day after injury. The frequency of this finding was higher than the frequency of reactive hepatitis detected in military personnel with digestive tract diseases (25%) who were in the ATO/JFO zone, did not sustain combat injuries, and were admitted for treatment to the gastroenterology clinic of the NVMCC "GVKG". Other digestive tract diseases in military personnel who sustained combat injuries were detected in isolated cases (non-alcoholic fatty liver disease (NAFLD) in 1.5%, hepatitis C (HC) in 2.5%). These rates were significantly lower than those obtained from the analysis of the structure of liver diseases in servicemen hospitalized from the ATO/JFO zone to the gastroenterology clinic of the NVMCC "GVKG" (NAFLD in 17.2-34.5%, HC in 9.7-43.5% of patients). The authors of the study concluded that the obtained results provide grounds for a thorough investigation of the functional state of hepatocytes in the wounded, with the aim of early detection of reactive hepatitis and its pathogenetic correction [2].

The increase in the number of injuries and the potential rise in the number of military personnel with liver and hepatobiliary system diseases necessitate the development of safe medicines that can be used by patients over extended periods without medical supervision. Such medicines may include plant-based remedies derived from fixed combinations of herbal preparations. This is because, in addition to their broad and predictable spectrum of pharmacological action, such remedies are relatively safe and do not require medical supervision.

Purpose. To study and analyse the results of pharmacological studies of herbal substances and their preparations with regards to hepatoprotective, hepatoregenerative, choleric, and antispasmodic

effects. To determine the conceptual composition of a combination of herbal medicinal products for use in the treatment of hepatobiliary system disorders in military personnel.

Materials and Methods. The bibliosemantic method was used in conducting the research. The study materials included scientific publications in professional journals.

Results of the Study and Discussion. The use of plant-based medicines has been the subject of research since ancient times. Many plant species can be beneficial in the treatment of a wide range of diseases. One such species that has played a significant role in medicine for centuries is milk thistle (*Silybum marianum* (L.) Gaertn.). The primary active component of milk thistle is silymarin, an extract obtained from the plant's fruit. Silymarin consists of seven flavonolignans (silibinin A and B, isosilibinin A and B, silychristin, isosilychristin, and silydianin) and a flavonoid (taxifolin) [18, 42].

Silymarin acts as an antagonist in various models of liver injury, including those induced by phalloidin and α -amanitin, lanthanides, carbon tetrachloride, galactosamine, thiocetamide, and the hepatotoxic FV3 virus. The therapeutic activity of silymarin is based on two key mechanisms of action: (1) stabilising the structure of the outer membrane of hepatocytes to prevent toxin penetration into the cell, and (2) stimulating the activity of nucleolar polymerase I, leading to increased ribosomal protein synthesis, thereby enhancing liver regeneration and promoting the formation of new hepatocytes [12].

The main component of Silymarin is the flavonolignan silibinin (silybin). It is present in the composition as two diastereoisomeric compounds: Silibinin A and Silibinin B, and is the most active constituent of this extract. The structure of silibinin consists of two main moieties. The first one is derived from taxifolin, while the second is a phenylpropanoid unit, which in this case is coniferyl alcohol. These moieties are interconnected into a single structure by an oxirane ring [11, 44].

Since the 1970s, conventional medicine has recognised silibinin as a compound with hepatoprotective properties. It also exhibits exceptional neuroprotective, antitumour, antioxidant, immunomodulatory, and anti-inflammatory activities and has been the subject of comparative studies with other flavonoids [26, 37]. Due to its anti-inflammatory, antioxidant, and antifibrotic effects, silibinin is used in the treatment of various liver diseases, including chronic conditions such as cirrhosis and hepatocellular carcinoma [22]. Moreover, in several in vitro and in vivo models, it has demonstrated significant inhibitory effects on various tumour types, including breast, renal, bladder, lung,

colorectal, and hepatic tumours [14, 27, 43]. However, its low aqueous solubility, reduced bioavailability, and short half-life significantly limit its therapeutic efficacy [29].

Owing to its antioxidant properties, silymarin has been investigated as a potential treatment for non-alcoholic steatohepatitis (NASH). One study aimed to evaluate the safety and efficacy of high-dose silymarin in patients with NASH without liver cirrhosis. This randomized, double-blind, placebo-controlled, multicenter phase II trial, conducted across five medical centers in the United States, assessed a patented, standardized silymarin preparation (Legalon®, Rottapharm | Madaus, Mylan). Patients were randomized to receive 420 mg, 700 mg, or placebo three times daily for 48 weeks. The results demonstrated that while high-dose silymarin was safe and well tolerated, its efficacy in NASH remained inconclusive. According to the authors, further clinical investigations are required to substantiate silymarin's potential in this context [45].

Studies investigating the antioxidant effects of silymarin in reducing hepatic complications associated with fingolimod treatment in patients with relapsing multiple sclerosis (MS) have demonstrated a significant reduction in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, a decrease in key pathogenic factors in MS, including malondialdehyde, and a significant increase in total antioxidant capacity and total thiol groups in the serum of patients treated with silymarin compared with the placebo group. These findings suggest the potential therapeutic role of silymarin in multiple sclerosis and its ability to reduce hepatic adverse effects associated with fingolimod therapy [5].

Based on available experimental data, the Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) has assigned the status of "traditional use" to the European Union herbal monograph for milk thistle fruits (European Union herbal monograph on *Silybum marianum* (L.) Gaertn, fructus). According to this monograph, the following herbal preparations are acceptable for traditional use in herbal medicines to support liver function and for the symptomatic relief of dyspepsia, including sensations of fullness and digestive discomfort: crushed plant material; dry extract (DER 30-40:1) with ethanol 96% (v/v) as the extractant; thick extract (DER 10-17:1) with ethanol 60% (v/v) as the extractant; dry extract (DER 20-35:1) with ethyl acetate as the extractant; dry extract (DER 26-45:1) with ethyl acetate as the extractant; dry extract (DER 20-70:1) with acetone as the extractant; dry extract (DER 20-34:1) with methanol 90% (v/v) as the extractant; and dry extract (DER 36-44:1) with ethyl acetate as the extractant. Single and daily doses

of these preparations for traditional use depend on the extractant employed and the DER ratio [10, 21].

According to the Commission E Monograph, the average daily dose of silymarin, expressed as silibinin, ranges from 200 to 400 mg. The preparation is recommended for the treatment of toxic liver damage and as maintenance therapy for chronic inflammatory liver diseases and cirrhosis [12].

In general, the findings of long-term research provide compelling and well-substantiated evidence supporting the feasibility of using standardized milk thistle extract for the treatment of liver diseases, particularly those of alcoholic etiology. Moreover, these studies confirm the good tolerability and safety profile of silymarin. The frequency of adverse reactions to the medication is low, and they are usually mild. Based on pharmacological and clinical data, it can be concluded that silymarin is safe, has therapeutic benefits, and is suitable for use as maintenance therapy for liver diseases, both as a monotherapy and as part of combination herbal medicines.

Artichoke (*Cynara scolymus* L.) is a perennial plant rich in various classes of phytochemicals, such as polyphenols, sesquiterpene lactones, and terpenoids [36]. Artichoke leaf extracts are rich in phenolic acids (caffeic acid, mono- and dicaffeoylquinic acid derivatives), flavones (glycosidic forms of luteolin and apigenin), anthocyanins (mainly glycosidic derivatives of cyanidin), and lower molecular weight phenolic compounds. Cynarin (1,3-di-O-caffeoylquinic acid) is considered one of the main biologically active secondary metabolites of artichoke [33, 38].

Epidemiological and pharmacological studies have demonstrated that artichoke has hypolipidemic, hepatoprotective, antitumor, antioxidant, and anti-inflammatory effects, as well as positive effects in the treatment of obesity [51].

The hepatoprotective activity of artichoke may be related to its antioxidant effect and the inhibition of Toll-like receptor 4 (TLR4) and the transcription factor NF-kappa-B (NF-kB), or the TLR4/NF-kB inflammatory pathway [47]. This, in turn, leads to the regeneration of dysfunctional liver cells [32] and exerts a therapeutic effect on the regulatory mechanism that allows DNA damage to be repaired in cases of hepatotoxicity [49]. This effect is demonstrated by a significant reduction in serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

The use of artichoke leaf extract in combination with metformin or vitamin E has shown beneficial effects on the liver in individuals with non-alcoholic fatty liver disease (NAFLD) [48]. Other studies have also reported that artichoke extracts improve NAFLD

in rodents [7, 50]. Scientific studies have demonstrated the choleretic effect of artichoke extract both in vivo [39] and in vitro [1].

A significant increase in bile flow was observed both after acute treatment with artichoke leaf extract and after repeated administration. The extract's effects on increasing bile acids were significantly more pronounced than those of the reference compound, dehydrocholic acid. It has been reported that the hepatoprotective and anticholestatic effects of artichoke extract in vitro are mainly related to its phenolic compounds, while the inhibition of cholesterol synthesis is associated with flavones [6].

The application of artichoke leaf extract significantly reduces serum LDL, total cholesterol, and triglycerides, indicating its positive effects on lipid profiles in the treatment of dyslipidemia and atherosclerosis [41]. The intake of the extract in combination with metformin or vitamin E can improve lipid profiles in individuals with non-alcoholic fatty liver disease (NAFLD) [48]. It has also been reported that artichoke extracts can reduce levels of triglycerides, total cholesterol, and LDL while increasing HDL [50]. Artichoke extract has been shown to improve HDL levels and reduce the total cholesterol to HDL ratio in a cohort of 20 individuals with mild hypercholesterolemia [30]. Screening of the main components of artichoke leaf extract revealed that cynaroside and, in particular, its aglycone luteolin are the primary factors inhibiting cholesterol synthesis in the body, compared to the less active chlorogenic and caffeic acids and cynarin [23].

The antioxidant activity of artichoke extract is mediated by an increase in liver protective enzymes (superoxide dismutase, catalase, glutathione peroxidase) against free radicals, as well as a decrease in the levels of malondialdehyde in the liver and plasma [40]. The antioxidant and anti-inflammatory effects of artichoke extracts are associated with their polyphenolic compounds [16, 17, 35, 46]. Consequently, artichoke has a wide range of applications due to its antioxidant and anti-inflammatory properties.

Based on the available experimental data, the Committee for Herbal Medicinal Products (CHMP) of the European Medicines Agency (EMA) has approved the 'traditional use' status of the EU monograph for the leaves of *Cynara cardunculus* L. (syn. *Cynara scolymus* L.), folium. According to this monograph, the following herbal preparations are acceptable for traditional use in herbal medicinal products for the symptomatic relief of digestive disorders such as dyspepsia with a feeling of fullness, bloating, and flatulence: crushed dried leaves for making teas; powdered leaves; dry extract of dried leaves (DER 2-7.5:1), extractant: water; dry extract of fresh leaves

(DER 15-35:1), extractant water; thick extract of fresh leaves (DER 15-30:1), extractant water; thick extract of dried leaves (DER 2.5-3.5:1), extractant ethanol 20% (v/v). Single-dose and daily doses of such preparations for traditional use depend on the extractant used and the DER. Because artichoke preparations stimulate bile secretion, they are not recommended for use in cases of cholelithiasis and biliary obstruction [8, 19].

According to the Commission E Monograph, the average daily dose of artichoke preparations should be equivalent to 6 g of fresh or dried leaves of *Cynara scolymus* (L.). Owing to their choleretic effects, these preparations are recommended for use in dyspeptic disorders [12].

The results of the reviewed studies demonstrate the hepatoprotective, hepatoregenerative, and anticholestatic effects of artichoke leaf extracts. The beneficial effect of the extracts on lipid profiles reveals their potential in the treatment of dyslipidemia and cardiovascular diseases. It is assumed that the indicated therapeutic activities are mediated by phenolic compounds, particularly cynarin. In general, based on pharmacological and clinical data, it can be concluded that artichoke leaf extract is a safe and therapeutically useful medication. It can be recommended for use as supportive therapy for liver and biliary tract diseases, both as a monotherapy and as part of combination herbal medicines.

Considering the previously described hepatoprotective properties of silymarin and the choleretic activity of artichoke preparations, a logical addition to the combination could be an ingredient with antispasmodic effects, which would facilitate the excretion of secreted bile in cases of spastic disorders of the gallbladder and bile ducts. A potential component of the combination could be Peppermint (*Mentha piperita* L.), whose preparations are widely recognized in global medicine for their antispasmodic and choleretic properties [9].

The chemical composition of mint leaves varies depending on the variety, ripeness of the plant, growing conditions, and processing. The composition of fatty acids in the non-polar lipid fraction is dominated by palmitic acid (16:0), linoleic acid (18:2), and linolenic acid (18:3) [31]. The flavonoid fraction is represented by luteolin and its 7-glycoside, rutin, hesperidin, eriocitrin, and highly oxygenated flavones. Other components include phenolic acids and small amounts of triterpenes [28, 34].

Peppermint (*Mentha piperita* L.) – was the first plant to be tested for use in the treatment of abdominal pain associated with irritable bowel syndrome [25]. This application is owing to the ability of peppermint preparations to relax smooth muscle

throughout the intestinal tract. The antispasmodic properties of peppermint are primarily associated with its essential oil and menthol, a component capable of blocking calcium channels [13].

Peppermint leaves have been shown to possess potent antioxidant properties in vitro, exhibiting free radical scavenging activity. This was also reflected in their iron chelating activity and inhibition of LDL cholesterol oxidation and DNA cleavage. The compounds responsible for these actions included both phenolic acids and flavonoids [15].

However most of the studies conducted have focused on the pharmacological properties of the essential oil, the traditional long-term use of other mint leaf preparations (hydroalcoholic or aqueous extracts) in gastroenterological practice deserves attention and further study.

According to the Commission E Monograph, peppermint preparations in a daily dose equivalent to 3-6 g of leaves are recommended for use in spastic disorders of the gastrointestinal tract, gallbladder, and bile ducts. In a fixed combination with Artichoke leaves and Dandelion root, mint leaf preparations are recommended for use in epigastric discomfort caused by functional disorders of the biliary system. In this case, the dose of the Mint preparation should correspond to 100% of that specified in its separate monograph, while the dose of the other components should be 50-75% of the dose specified in the corresponding monographs of the individual plants [12].

The Herbal Medicinal Products Committee (HMPC) of the European Medicines Agency (EMA) has classified the following mint preparations as being in traditional use: crushed plant material for tea, tincture (1:5; ethanol 45% v/v), and tincture (1:5; ethanol 70% v/v). The recommended daily dose of

mint in tea is equivalent to 4.5-9 g of leaves and 6-9 ml of tincture [20].

Conclusions

1. Established that injuries can have significant effects on function and condition of the hepatobiliary system. Accordingly, the increase in the number of injuries and the potential rise in the number of military personnel with liver and biliary tract disorders necessitate the development of safe medicines.

2. It is determined that, due to their broad and predictable spectrum of pharmacological action combined with safety during prolonged use, combined plant-based medicines can effectively be applied in clinical practice.

3. Is it established that, for the development of a combination medicinal product, it is advisable to use preparation from the Milk thistle (*Silybum marianum* (L.) Gaerth.), Artichoke (*Cynara scolymus* L.) and Peppermint (*Mentha piperita* L.). According to the results of research, extracts of these substances are able to provide hepatoprotective, hepatoregenerative, choleric, and antispasmodic effects in the finished medicinal product.

Prospects for further research. Based on the analysis on the results of pharmacological studies of herbal substances and their preparations, the data indicate the potential for their practical use in the treatment of hepatobiliary system disorders in military personnel. From a technological perspective and taking into account the experience of traditional application of plant monopreparation, it is most appropriate to use their dry extract within combination. The next stages of research should include the development of the composition and technology of the finished medication as well as its target quality profile.

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