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THE USE OF HERBAL REMEDIES IN THE TREATMENT OF HEPATOBILIARY DISEASES: TRENDS AND PROSPECTS

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Hepatobiliary system diseases represent an important medical and social problem due to increasing morbidity rates worldwide. Liver and biliary diseases are characterized by complex pathophysiology as well as by multi- and comorbidity. The treatment of such diseases necessitates multitarget drug development. The effectiveness of current drugs in the treatment of hepatobiliary disorders remains low and the incidence of side-effects are profound. This actualizes the search and development of highly effective hepatoprotectors with a low incidence of side effects. Medicinal plants potentially constitute a sourse of such preparations. The review summarizes the data concerning mechanisms of hepatoprotective and immunomodulatory effects of medicinal plants and their phytoconstituents. The prospects for the development and use of herbal remedies in the treatment of hepatobiliary diseases are outlined.

Key words: hepatobiliary diseases, medicinal plants, hepatoprotectors, immunomodulators.

Digestive system diseases (DSD) are among the most common pathologies of internal organs, found in 10 to 15% of population of the developed countries [1, 2]. Usually, the anatomically and functionally related systems and organs are involved in the pathological process of these diseases. For many years, the prevention and treatment of DSD have been one of the most important medical problems. The most frequent pathological conditions of the digestive tract are diseases of the hepatobiliary system. In particular, the diagnosis of hepatobiliary disorder is among the top 100 in the US and many European countries. As of 2018, hepatobiliary pathology accounts for more than a quarter of cases per year of all DSD in USA [3–5]. According to WHO, more than 2 billion people worldwide suffer from the pathology of the hepatobiliary system, 100 times the number of patients with HIV. Annually, 500 000 to 1 million patients with liver, gallbladder and biliary tract diseases are registered in the Commonwealth of Independent States. In Ukraine, the pathology of the hepatobiliary system is 60.32% of all DSD. The prevalence of that pathology increased by 20.1% in Ukraine in the latest decade [6, 7]. Diseases of the hepatobiliary system include a wide range of pathological conditions of the liver, gallbladder and biliary tract of infectious and non-infectious etiology. The liver diseases are classified into diseases related to malformations, hereditary diseases, and chronic diseases which account for the largest share. Chronic types of hepatitis are of viral, congenital or autoimmune nature, and take the leading place among chronic liver diseases. Pathological conditions of the biliary system include diseases caused by birth defects of the gall bladder, and diseases of the biliary tract. Those, in turn, are divided into functional disorders in the

forms of dyskinesias of hypotonic, hypokinetic and hyperkinetic types, and cholecystitis, cholangitis and cholelithiasis [8]. The cholelithiasis is the most costly hepatobiliary disease. Medically, it involves the formation of concretions in the gallbladder due to the abnormally high cholesterol or bilirubin (heme breakdown product) in bile [9]. Almost 20% of adult Europeans, and nearly as many Asians have gallstones. Cholelithiasis is mostly found in female patients. It is a chronic state, with prevalence increasing with age (reaching plateaus after the ages of 50 and 60 in women and men, respectively). Hence, highly prevalent cholelithiasis in the elderly people is considered to be one of the most serious medical problems of the contemporary aging human population. In addition, cholelithiasis is also a major cause of gallbladder carcinoma, which is fifth of the most common cancers and has an extremely high patient mortality rate. The main reasons for the increasing prevalence of cholelithiasis are the dominance of high-calorie diets combined with a general decrease in physical activity [10–13].

Diseases of the hepatobiliary system (HBD) can occur in acute and chronic forms, as well as be accompanied or cause a number of threatening conditions with characteristic symptoms and syndromes: jaundice, portal hypertension, hepatic coma, hepatic insufficiency, cirrhosis, general intoxication [14, 15].

The aforementioned suggests that functional disorders of the liver and biliary tract are one of the most important problems for healthcare professionals worldwide. Different groups of pharmaceuticals are used in the complex treatment of HBD, but special place among the medical preparations are those with a selective effect on the liver, hepatoprotectors. The mechanisms of direct protective action of most hepatoprotectors are not yet fully understood. However, they are known for their membrane-stabilizing, antitoxic, anti-inflammatory, choleretic, antiviral, antioxidant, immunomodulatory and other effects [16, 17]. Hepatoprotective preparations normalize metabolic processes and homeostasis in the liver, increase the resistance of hepatocytes to pathogenic effects, stimulate regenerative processes, restore the liver parenchyma and normalize its physiological functions. However, the existing hepatoprotective preparations for the treatment of HBD are still poorly effective, primarily due to the side effect caused by toxic chemicals [18, 19]. Hence, medicines with low or no side effects are needed, which incited research that is aimed at finding and developing effective hepatoprotective herbal remedies [20–24].

Polyherbalism in phytotherapy

Phytotherapy (PT) is a form of complementary and/or alternative medical practice [25]. It is usually implemented with the common treatment, not instead of it [26]. Today the share of phytopreparations in the world pharmaceutical market is over 40%. According to WHO, this proportion will increase to 60% of the total list of medicines over the next ten years. The fact that the Nobel Prize in Physiology and Medicine in 2015 was awarded to Tu Youyou, William C. Campbell and Satoshi Omura for the discovery of natural products for the treatment of tropical parasitic diseases is in favor of the progressive development of phytopharmacology [27, 28].

There is a plethora of crude drugs derived from medicinal plants which are used in the treatment of various human diseases and ailments. For a systemic study of crude plant-derived medications it is very important to classify them in proper system. There are several classifications of crude plant-derived drugs: alphabetical cassification (crude phytopreparations are arranged alphabetically either in Latin name or in English name); taxonomical (botanical) classification (phytopreparations are arranged in a group according to their division, class, order, family, genus and species); morphological classification (phytopreparations are arranged in a group according to the used part of plant, e.g. flower, root, etc.); pharmacological classification (phytopreparations are grouped according to their pharmacological action, e.g. anticancer, anti-inflammatory, antibacterial, etc.); chemical classification (phytopreparations are classify according to their content of active substances, e.g. alcaloids, volatile oils, etc.). Additionally, all phytopreparations are divided into three broad categories (Fig. 1): preparations based on dried raw materials (compositions of collected plants, briquettes); extraction preparations; preparations composed by separate fractions of raw materials (juices, oils). Extraction preparations, in turn, are divided into galenic, neogalenic, and preparations of individual biologically active compounds (BAC) of plant or more complex origin. Galenic formulations are preparations which have a complex chemical composition and are a product of treatment of herbal medicinal raw materials for preservation of BAC in the native state.

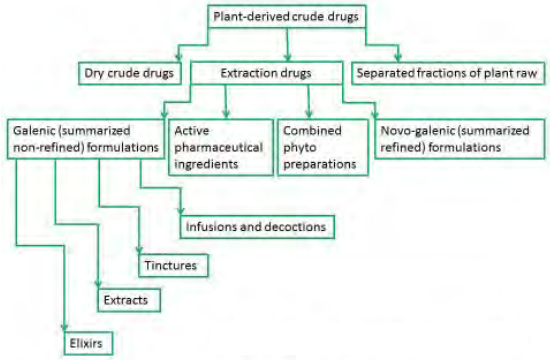

Fig. 1. **Classification of plant-derived crude drugs**

Neogalenic formulations are mixtures of active substances of plants, purified from ballast and related substances. Complex preparations, in addition to plant BAC, may include chemical constituents. Galenic preparations, in turn, are divided into infusions and decoctions, tinctures, extracts (liquid, thick and dry), and preparations from fresh raw materials. By the method of implementation of drugs in PT, the preparations can be divided into those intended for internal and external application. The liniments (balms), ointments, creams, and compresses are intended for external use.

Plant extracts are the base of all herbal preparations for internal use. The extracts separate the useful (medicinal) components from the fibrous, less useful part of the plant. Tinctures are highly concentrated, mostly alcohol-based extracts of fresh or dried plants. Most BAC of medicinal plants are soluble in alcohol, thus this way of separating them from the plant is the most effective. Elixirs are tinctures with the addition of sweeteners. Extraction can be also realized from an herbal tea, which is the most popular, simplest and least concentrated aqueous extract of medicinal plants. The use of herbal extracts in a tea preparation is ideal for chronic conditions, including HBD, when long-term exposure to BAC of medicinal plants in low concentration is desirable. Among tea preparations, there are decoctions and infusions. Infusions are mostly prepared from the above-surface plant parts (flowers, leaves), by treatment of plant material with boiling water and letting it steep for a varying period of time to obtain drugs with different BAC concentrations. Not only flowers and leaves, but also seeds, roots and bark are used to make decoctions. In that case, raw plant material is added to cold or boiling water and maintained at a temperature of 50–100 °C also for different time intervals [29–31].

An important element of the development of PT is the development of complex herbal products based on mixtures of medicinal plants. This is due to the increasing level of comorbidities (coexistence of two or more syndromes or diseases in one patient, pathogenetically interrelated or coincidental) and polymorbidities (presence in the individual of several diseases having synchronous course in different phases and stages, both related and unrelated genetically and in their pathogenesis) in current therapeutic practice [32–36]. The comorbidity is also characteristic of HBD [37–39]. The simultaneous presence of several pathological conditions, as well as complex pathophysiology of many diseases, including HBD, dictates the need for using BAC of medicinal plants with biological action of different nature. This requires an in-depth study of the biological effects of herbal mixtures, and the possible synergism and antagonism of herbal BAC in their composition. The multicomponent mixtures of medicinal plants are preferable because of the proven fact of synergistic and additive action of plant BAC in the certified and newly created polyherbal compositions. Recently, the traditional “one drug, one target, one disease” approach in the development of preparations and treatment strategies has become increasingly replaced by a new approach, the therapy combining the use of several active substances. This change in priorities is partly due to the limited therapeutic efficacy of mono-component treatment of poly-etiological diseases that have complex pathophysiology, such as cancer, neurodegenerative diseases, diabetes, most chronic diseases, including liver and gall bladder disorders, etc. Another reason is the development of drug resistance in case of mono-component therapy, as well as the side effects of synthetic monopreparations [40–42]. In addition, the development of analytical chemistry and molecular biology techniques has broadened our understanding of the therapeutic targets of many diseases and multicomponent therapeutic approaches. Phytotherapeutic medical systems also use multicomponent herbal remedies in many cases, as numerous studies have proven their superior efficacy compared to single medicinal plants [43, 44].

Herbal preparations in the pathogenetic treatment of hepatobiliary diseases

The use of herbal remedies in the treatment of HBD worldwide is considered as an alternative to existing pharmaceuticals because of the formers’ safety, availability, cost-effectiveness, and therapeutic efficacy [45]. IUCN has proposed the use of about

50000 to 80000 flowering plants for medicinal purposes, many of which are used in the treatment of liver disease, gallbladder and biliary tract ailments. According to the literature, about 35% patients suffering from chronic HBD prefer to use herbal remedies for treatment, and more than 60% use herbal remedies in combination with synthetic drugs [46, 47]. The main directions of phytotherapy for HBD are rehabilitation after acute diseases, treatment of exacerbated chronic diseases, prevention of possible relapses of liver and biliary diseases, restoration of disturbed metabolic processes (in steatosis and steatohepatitis of different etiology, post-cholecystectomy syndrome, etc.), reduction of side effects of chemotherapy, and restoration of reduced overall reactivity of the body due to adverse environmental factors.

According to numerous literature data and our own results, hepatoprotective properties have been found in plants of many families (Fig. 2), most often *Acanthaceae, Amaranthaceae, Asteraceae, Cyperaceae, Euphorbiaceae, Fabaceae, Primulaceae, Rosaceae, Rutaceae, Schisandraceae, Scrophulariaceae, Solanaceae, Utricaceae*, and many others [48–52]. Constituents of medicinal plants with hepatoprotective properties are mainly secondary metabolites produced by the plant against herbivores, phytopathogenic microorganisms, insects and competing plants [53].

The most well-known hepatoprotective plant constituents (Fig. 3) include numerous phenolic compounds, including flavonoids, terpenoids or terpenes, alkaloids and some others [53, 54].

Most publications on the hepatoprotective properties of plant constituents concern polyphenolic compounds. Plant polyphenols have various pharmacological effects on oxidative stress, lipid metabolism, insulin resistance and inflammation, which are the most important pathological processes in the etiology of liver disease [55]. This puts the polyphenols in the spotlight when looking for phytotherapeutic drugs to treat HBD. High content of polyphenols is present in many vegetables (soy, pepper) and fruits (pomegranate, guava, peach), tea and a large group of medicinal plants. Phytophenol compounds include several classes of substances: *flavonoids* (flavones, such as luteolin; flavonols, such as quercetin; flavanone, for example, hesperidin, and flavanonols, including taxifolin), *biflavonoids* or dimers of flavonoids (for instance, bilobetol), *isoflavones* (such as genistein), *chalcones* (e.g., phloretin), *phenolic acids* (among which there are two classes, benzoic and cinnamic acid derivatives). Hydroxybenzoic acids include gallic, ρ-hydroxybenzoic, protocatechuic, vanilla and syringic acids [56]. Hydroxycinnamic acids are more common than hydroxybenzoic and are composed mainly of ρ-coumaric, caffeic, ferulic and sinapinic acids [57], as well as esters of caffeic acid with chlorogenic acid, and 2-hydroxyhydrocaic acid (rosemary acid), capable of hydrolysis and condensed tannins, lignans and stilbenoids.

Antioxidant action is the most important hepatoprotective mechanism of phenolic compounds inherent in a wide range of medicinal plants. Plant phenolic compounds normalize the enzymatic activity of liver cells, maintain the balance of the oxidant-antioxidant system, as well as can selectively activate apoptosis of malignantly transformed cells. The biological activity of plant phenolic compounds depends on the method of their extraction and composition, the dose dependence of the effects of these drugs varies greatly depending on the type of compound and is still under investigation [58, 59].

The polyphenolic plant compounds with hepatoprotective action which attract the most attention are flavonoids, the largest

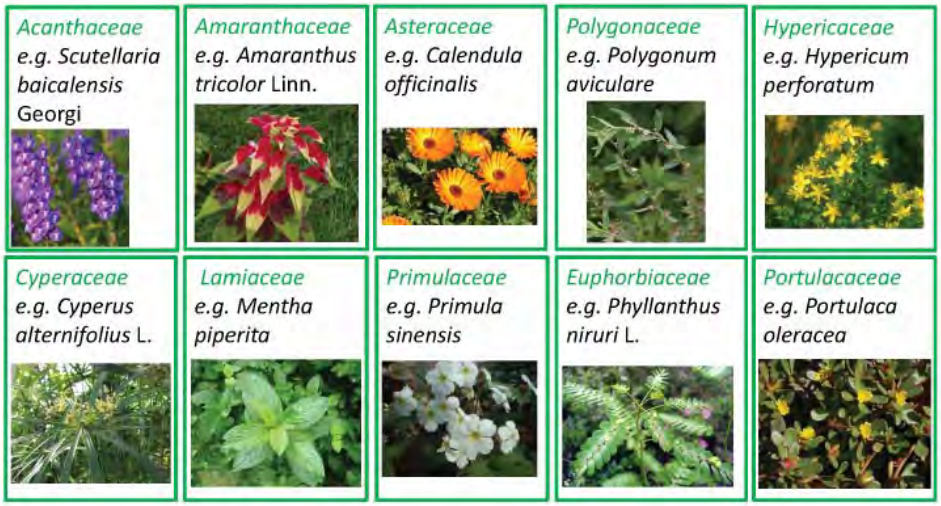

Fig. 2. **Commonly used medicinal plants with hepatoprotective properties**

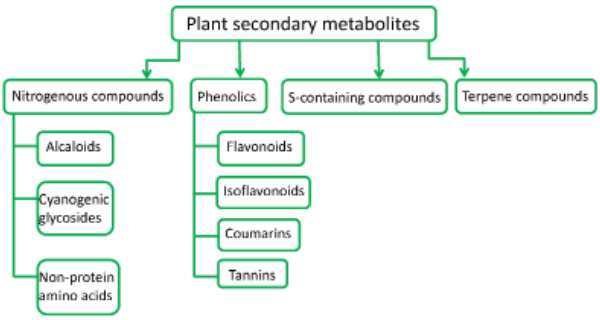

Fig. 3. **Plant secondary metabolites**

class of plant polyphenols. More than 6000 plant flavonoids have been described. Plant flavonoids are characterized by significant structural diversity, high multifaceted biological activity and low toxicity. Herbal flavonoids have a wide range of pharmacological properties: antioxidant, angioprotective, hepatoprotective, choleretic, diuretic, neurotropic, etc. It is medicinal plants containing flavonoid compounds that are considered to be the most promising source for the creation of herbal preparations. In view of this, numerous attempts have been made to systematize and classify plant materials containing flavonoids. One such classification is proposed by pharmacologists of the Samara State Medical University, according to which medicinal plants that accumulate flavonoids are divided into pharmacopoeial plants containing flavonoids as a leading group of BAC (immortelle, pigweed, etc.), pharmacopoeial essential oil plants containing flavonoids (yarrow, peppermint, etc.), pharmacopoeial plants containing bitter compounds and flavonoids (dandelion, plants of the genus *Leonurus*, etc.), pharmacopoeial plants containing saponins and flavonoids (licorice, horse chestnut, etc.), pharmacopoeial plants containing vitamins and flavonoids (calendula, tickweed, rosehips, etc.), pharmacopoeial plants containing simple phenols and flavonoids (sharp-leaf willow, etc.), pharmacopoeial plants that contain tanning substances and flavonoids (bird cherry, blueberries, etc.) and pharmacopoeial plants containing alkaloids and flavonoids (celandine, etc.) [60].

One of the most widely used and thoroughly researched herbal hepatoprotective flavonoid drugs are flavonoid lignans of *Silybum marianum*, known as silymarin and characterized by distinct antioxidant, cytoprotective and anticarcinogenic properties. In addition, the antiviral properties of silymarin have been reported in patients with viral hepatitis. Silymarin has also been shown to be effective in patients with non-alcoholic liver steatosis, where it has a potent antioxidant effect, stabilizes hepatocyte membranes, and restores mitochondrial function [61, 62]. The membrane-stabilizing effect of the thistle flavonoids is also due to the fact that silibinin, the basic BAC of silymarin, is able to interact directly with hepatocyte membranes [63].

Catechins, the flavonoid components of green tea, can stimulate the synthesis of antioxidant defense enzymes, such as glutathione transferase (GT) and superoxide dismutase (SOD), thereby realizing their hepatoprotective effect [64].

Luteolin, a flavone of weld, can enhance the activity of antioxidant defense enzymes and modulate the synthesis of xenobiotic metabolizing enzymes [65].

Genistein, a legume isoflavone, is capable of regulating NFκB-dependent signaling and thus influences the synthesis of many inflammatory mediators. The flavonone naringenin, found in many citrus fruits, as well as flavonol quercetin, are capable of the same effect [55]. Polyphenolic compounds such as resveratrol (stilbenoid), curcumin etc. can activate apoptosis of malignantly transformed cells, including liver carcinoma cells, possess antifibrotic properties, activate numerous signaling cascades involved in the regulation of lipidoximidoxide oxidase [66].

It is also traditional to use glycyrrhizin (saponin, contained in the roots of licorice) to treat pathologies of hepatobiliary system. This herbal remedy has been used for many years in disorders of liver function associated with obesity, as well as in the treatment of non-alcoholic liver steatosis. Numerous animal models have shown that glycyrrhizin is capable of reducing hepatic lipogenesis, has antioxidant activity, and restores insulin sensitivity [67, 68].

Terpenoids are divided into hemiterpenes, monoterpenes, sesquiterpenes, diterpenes, triterpenes, tetraterpenes and politerpenes. Terpenoids are widespread in medicinal plants and are part of essential oils and resins. Terpenoids include saponins, steroid compounds, triterpene bitternesses, carotenoids, rubber and gutta-percha. The ether-bearing plants that accumulate terpenoids are representatives of *Lamiaceae, Cupressaceae, Pinaceae, Apiaceae, Brassicaceae, Myrtaceae, Asteraceae and Rosaceae*. Essential oils can accumulate in flowers, fruits, roots and wood of plants. Plant bitternesses are represented mainly by monoterpenoid iridoid

glycosides and accumulate in *Valerianaceae, Lamiaceae, Scrophulariaceae, Plantaginaceae*, etc. Sesquiterpene bitternesses are found in yarrow and wormwood. The most common plants containing terpenoids are anise, mountain arnica, birch, valerian, goldenrod, coriander, medicinal dandelion, oregano, peppermint, sage medicinal and some others [69]. Powerful hepatoprotective properties are observed in tetracyclic terpenic saponins such as dammarane (found in *Apiaceae*), derivatives of lanostane and cycloartan (in *Ranunculaceae*), cucurbitan (accumulates in *Cucurbitaceae*), as well as pentacyclic terpene glycosides, which are found in *Lamiaceae* and have the lowest level of hepatotoxicity [70].

Much attention has been paid in recent years to herbal terpene hepatoprotective preparations with andrographolide, a labdane diterpenoid, which is the main biologically active component of the medicinal plant *Andrographis paniculata* and known a "king of bitterness" for its exceptional taste. In addition to hepatoprotective properties, this phytoconstituent has powerful antioxidant properties, antidiabetic, antiviral, antibacterial, antimalarial and antiatherosclerotic effects. It is considered by experts in the field of pharmacology as a substrate for a number of preparations with anti-inflammatory properties [71, 72].

As for plant alkaloids, hepatoprotective activity has been reported for phylantine, a compound from *Phyllanthus niruri*, plant of the family Phyllanthaceae. It is capable of antioxidant activity and in animal model studies has demonstrated the ability to restore enzyme homeostasis [73]. One of the most famous barberis alkaloids, berberine, is also used in the treatment of HBD and has choleretic and antispasmodic effects. This alkaloid lowers the viscosity of bile and promotes bile excretion, reduces the tone of the gallbladder smooth muscle, and reduces the amplitude of its contractions [74, 75].

For the treatment of disorders of the biliary system, the most commonly used preparations are herbal choleretic drugs, which are divided into choleretics (enhancing the formation of bile by the liver), cholekinetics (stimulating the reduction of the gallbladder) and spasmolitics (increasing the excretion of bile by removing spasm of bile ducts) [76]. To date, more than 100 medicinal plants whose preparations can be used as choleretics have been described in the literature. Medicinal plants with choleretic properties can be divided into the following groups by the mechanism of action: 1) medicinal plants with choleretic properties (cumin, yarrow, calendula, mint, corn stalks, roots and stalks of dandelion and rose, etc.); 2) medicinal plants with anti-inflammatory action (plants of the genus *Hypericum*, buckthorn, chamomile, yarrow, nettle, etc.); 3) medicinal plants used against the biliary tract dyskinesia of hypertonic type (valerian, belladonna, chamomile, barberry, etc.); 4) medicinal plants used in dyskinesia of the biliary tract of hypotonic type (peppermint, thyme, tansy, etc.) [77].

It is quite difficult to classify medicinal plants that affect only the liver or only the bile ducts. The reason is that each plant affects several components of the hepatobiliary system. There are plants that affect mainly the liver parenchyma, others may affect mainly the excretion of bile, some have mainly antispasmodic effect. On the other hand, there are medicinal plants with choleretic and cholelitic action, which in addition have a bacteriostatic or bactericidal effect, thus they can be used as complementary preparations in the treatment of cholangitis and cholecystitis [78].

To conclude that review on the use of medicinal herbs in the pathogenetic treatment of HBD, it should be noted that phytotherapy in case of chronic liver and biliary tract diseases usually lasts for several months. Usually, complex herbal remedies are utilized containing multiple medicinal plants with synergistic and/or additive action, or several different medicinal plants are used sequentially [79]. The principal hepatoprotective mechanisms of herbal remedies are mainly to restore normal levels of liver enzymes in serum, including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and enzymes of antioxidant protection, as well as total bilirubin and total protein levels. The choleretic influence of medicinal plants includes effects on both the formation and secretion of bile [80].

Prospective directions in the search for new herbal hepatoprotective agents are the creation of medicinal plants compositions that contain BAC complementing each other without causing toxic effects.

Immunomodulatory effects of medicinal plants

One of the most important mechanisms of hepatoprotective action of medicinal plant preparations is the influence of their constituents on various components of the inflammatory response. The ability to modulate immune reactivity is one of the most significant manifestations of the biological activity of herbal remedies. The

function of the immune system is closely linked to the general state of human health, so the pathogenesis of many diseases involves disorders of the immune reactivity. Local and systemic inflammation is an important component of the pathophysiology of diseases of the hepatobiliary organs [81–84] (Fig. 4). However, it is still rare to incorporate medicinal plants with immunomodulatory properties into polyherbal remedies in medical practice. It is more common in experimental studies [85–87]. In the modern society, there is a significant proportion of persons of working age with compromised immune reactivity, that is, with abnormally functioning effector mechanisms of both innate and adaptive immunity [88–90]. Immune reactivity disorders, associated with many diseases (including HBD), as well as the compromised immune system of otherwise healthy individuals require the development of safe and effective means of immunocorrection. Existing synthetic immunocorrectors (immunomodulators) have low therapeutic and prophylactic efficacy and cause a number of side effects, which, for instance, can adversely affect the functioning of some parts of the immune system. Thus, particular attention in recent years has been paid to the study of natural immunomodulators of microbial, animal and plant origin [91, 92].

Phytoconstituents of medicinal plants can exert immunosuppressive, immunostimulatory and homeostatic (normalizing) immunomodulatory effects. In addition, herbal remedies enhance the efficacy of the anti-infective chemotherapeutic agents in the treatment of infections [93, 94]. Due to immunostimulatory properties, herbal remedies have long been used as vaccine adjuvants [95]. In particular, the extracts of *Azadirachta indica* leaves and of ginseng root exhibit adjuvant activity in the composition of antitumor vaccines compared to those of the complete and incomplete Freund's adjuvant [96]. The most famous herbal adjuvants are saponins. Many of these biologically active substances are found in edible crops such as potatoes (α-solanine, α-chaconin) and tomatoes (α-tomatine). The ability of plant saponins to stimulate cellular immune responses is now considered in the prospect of developing so-called edible vaccines, a type of mucosal vaccines that are considered as an alternative to injected vaccines [97]. Vegetable proteins, such as carbohydrate-binding lectins, have adjuvant activity comparable to that of cholera toxin, which has been demonstrated in animal models using mucosal vaccines for intranasal administration [98]. The adjuvant action of the abovementioned herbal preparations is based on their ability to activate nonspecifically the functions of the immune system cells involved in the initiation of the immune response, such as macrophages, monocytes, and neutrophils. Genetically modified plant organisms are also used for the creation of antitumor vaccines. The extracts of such plants contain targeted tumor-associated and tumor-specific antigens, which are used not only to manufacture antitumor vaccine preparations, but also for the development of diagnostic test systems in oncology. Vaccines based on such extracts contain not only the transformed plant-targeted protein or DNA, but also the adjuvant biologically active substances synthesized by the plant [99, 100].

Echinacea is one of the herbs that have been used for a long time to restore compromised immune reactivity, including in childhood. The preparations of all existing species, *Echinacea angustifolia*, *Echinacea purpurea* and *Echinacea pallida*, are used to enhance suppressed immune reactivity. Echinacea preparations enhance the cytotoxic activity of macrophages and natural killer cells, activate the metabolism of neutrophils, stimulate the synthesis of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), IL-12, etc. [101, 102]. Extracts of root and aerial plant parts of *Echinacea purpurea* can significantly enhance the antigen presenting activity of dendritic cells by activating

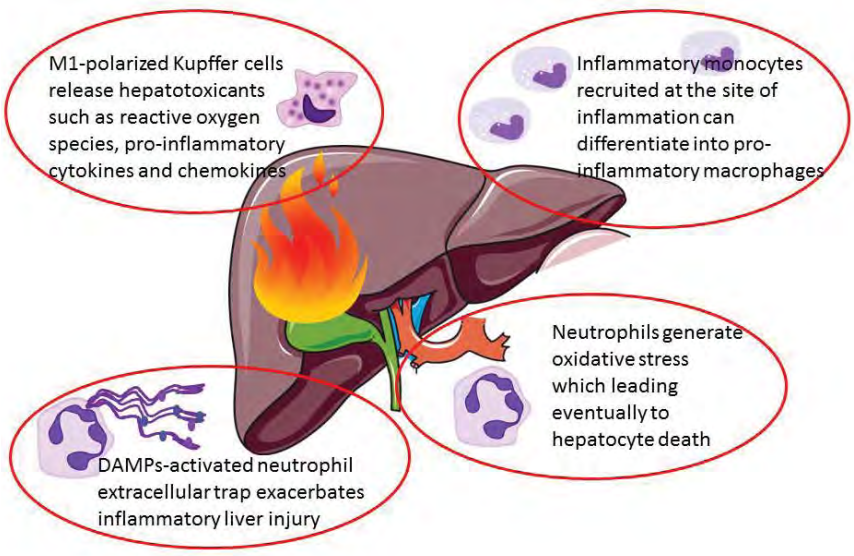

Fig. 4. **Innate immune cells in liver and gallbladder inflammation**

JNK, p38-MAPK and NF-κB-dependent signaling pathways [103]. Another example of the oldest used plants, whose preparations are characterized by a powerful immunostimulatory action, is garlic (*Allium sativum*). Garlic is called a "plant antibiotic" because of its antiseptic properties and anthelmintic effect. Garlic extracts contain more than 200 biologically active constituents, including about 33 sulfur-containing compounds, numerous enzymes, amino acids and minerals, for example, selenium. Aqueous extract of garlic has a dose-dependent stimulatory effect on the leukocyte oxidative metabolism and enhances the proliferative activity of T cells. Lectins, contained in raw garlic, affect the isotype switching of immunoglobulins, reducing IgE synthesis while enhancing IgG and IgM production. Garlic preparations (mainly aqueous fresh extracts and tinctures) are used to overcome stress-induced immunosuppression [104–106]. The immunostimulatory properties of ginseng (*Panax ginseng*) are also widely used. The saponins and glycosides from this plant have powerful adaptogenic properties. Ginseng extracts enhance the migration ability of leukocytes, including macrophages and T-cells, stimulate the synthesis of proinflammatory cytokines and plant factors such as IL-1, IL-2, TNF-α, granulocyte-macrophage colony-stimulating factor, etc., and enhance B-cell antibody generation and mitogen-induced proliferative activity of lymphocytes. Ginseng-based dietary supplements enhance vaccination efficacy by acting as mucosal adjuvants [107–109]. Powerful immunostimulatory properties are described for *Sambucus nigra*. Syrups and aqueous extracts of its berries, as well as teas based on it, stimulate the leukocyte migration to the foci of infection and increase the functional activity of myeloid cells in the acute phase of inflammation [112]. To enhance the suppressed immune reactivity, different forms of preparations can be used. They may contain extracts of different parts of one plant, selected individual BAC and their mixtures, as well as polyherbal phytopreparations, which include extracts or phytoconstituents of several plants. A wide range of commercial phytopreparations with immunostimulatory activity is introduced into the medical and veterinary practices, among which polyherbal compositions are predominant, with therapeutic and prophylactic action based on the synergistic action of BAC of various medicinal plants. Here are several examples of such drugs:

• ImmuPlus^{R} — polyherbal veterinary immunostimulatory drug comprising four medicinal plants: *Ocimum sanctum*, *Tinospora cordifolia*, *Emblica officinalis* and *Withania somnifera* [111].

• Echinacealiquid^{R} — polycomponent syrup, which includes extracts of three species of echinacea. Used to restore immune reactivity suppressed by prolonged infectious processes, etc. [112].

• Sambucol^{R} — a preparation, 38% of which is made up by a standardized elderberry extract, and the rest are polyphenolic compounds of other medicinal plants. It is used to enhance immune reactivity in patients with viral infections [113].

Many of phytopreparations have immunosuppressive activity, the action of which is aimed at controlling the inflammatory activation of the immune system. Often, a systemic inflammatory response syndrome (SIRS) may develop in the case of many diseases of inflammatory etiology, both infectious in nature (bacterial, viral, fungal diseases and infectious processes of mixed etiology), and aseptic inflammatory diseases (rheumatoid arthritis, diseases of the hepatobiliary system, metatabolic syndrome, sugar mellitus, gout) if the inflammatory process is generalized. SIRS is accompanied by cytokine storm which is the high level of synthesis of anti-inflammatory cytokines, possibly dangerous to the patient's life. The cytokine storm is particularly characteristic for viral infections caused by flu virus. The cytokine storm in this case is most often the cause of lethality [114]. Numerous studies have revealed the high efficiency of multicomponent herbal remedies in overcoming cytokine storms, especially in infectious diseases. The authors of these publications convincingly prove the synergistic effect of phytoconstituents of various medicinal plants in inhibiting the proinflammatory immune response and stimulating restorative, homeostatic immune responses [115]. As noted above, the vast majority of effective herbal immunomodulators are multicomponent drugs, and physicians that practice phytomedicine convincingly prove that the synergistic or additive effects of BAC of different parts of one plant or several in the composition of a complex preparation are fundamentally important for the drug's immunomodulatory activity and therapeutic efficacy. However, the evidence base for this assertion is still insufficient and requires an in-depth study of the immunomodulatory properties of complex herbal preparations with the ability to modulate immune reactivity to optimize their use in the complex treatment

of human pathology. The ancient recipes of multicomponent phytocompositions that have been used for a long time in Traditional Chinese Medicine or Ayurvedic practice have only recently been subjected to an analysis of their high efficiency mechanisms. In particular, the immunomodulatory effect of a mixture of black pepper (*Piper longum*) and ginger (*Zingiber officinalis*) is based on the ability of the piperine alkaloid contained in black pepper to increase the bioavailability of ginger phytoconstituents. The result of the high immunomodulatory efficacy of multicomponent herbal remedies can be more than a synergy (a more pronounced effect in the case of a combination of preparations in comparison with individual use). In some cases, the phytoconstituents of one of the components of the multicomponent preparation help to preserve the nativeness and biological activity of the other. For example, the antioxidant BAC contained in large quantities in valerian, garlic, or ginger extracts can help to preserve the integrity of the BAC of combined medicinal plants. Studies of ancient multicomponent phytopreparations have shown that their immunomodulatory activity is completely or substantially lost when they are fractionated or used in separate components. The mechanisms of high immunomodulatory activity of combinations of medicinal herbs such as bell pepper (*Piper methysticum*) and valerian (*Valeriana officinalis*), ginseng and ginkgo, are still under investigation [116, 117].

An example of a plant whose preparations have long been used in medical practice to control inflammation is *Glycyrrhiza glabra*. Phytochemical analysis of licorice preparations, carried out by numerous scientific groups, proved that the phytoconstituents responsible for the anti-inflammatory action of its preparations are saponins, flavonoids and pectins. Licorice preparations inhibit phospholipase A, enhance the synthesis of IL-10 and other anti-inflammatory cytokines, stimulate differentiation of regulatory T-cells, etc. [118, 119].

Curcuma longa L. also has potent anti-inflammatory activity. One of the mechanisms of action of turmeric BAC-based preparations is the inhibition of cyclooxygenase-2 and the stimulation of cytokine shift toward the predominance of Th2 type cytokines [120]. A herb with a pronounced anti-inflammatory effect is *Zingiber officinale*. More than 400 BAC have been found in ginger root, of which about 70% are carbohydrate compounds. Aqueous extracts of ginger root inhibit the lipoxygenase and cyclooxygenase activity of leukocytes, enhance the synthesis of anti-inflammatory and immunoregulatory cytokines, such as transforming growth factor-β (TGF-β) and IL-12. Dietary supplements which include ginger are effective in the complex treatment of peptic ulcer disease. It should also be noted that ginger preparations are capable of controlling Th2 inflammation which is characteristic to an allergic pathology [121]. The anti-inflammatory properties of *Nigella sativa*, which has only recently been adapted to cultivation in Ukraine, have been used for more than 2000 years. The anti-inflammatory immunomodulatory action of preparations and supplements based on this plant is realized due to the presence of polyunsaturated fatty acids in its composition, which inhibit the induced oxidative metabolism of mononuclear phagocytes, reduce the synthesis of eicosanoids and enhance production of anti-inflammatory and immunoregulatory Th2-profile cytokines [122]. Anti-inflammatory immunomodulatory activity is characteristic of herbal remedies based on cinnamon and aloe vera, hibiscus and calendula, chamomile, plants of the genus *Hypericum* and many other medicinal plants.

The anti-inflammatory immunomodulatory action is realized in phytoconstituents of medicinal plants due to numerous different mechanisms. For example, alkaloids of *Corydalis turtschaninovii* Besser are able to inhibit the phosphorylation of ERK and p38, resulting in the inhibition of NFκB-dependent signaling pathways and the reduction of the synthesis of proinflammatory mediators such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), TNF-α, IL-6, IL-1β, etc. The essential oils of many medicinal plants are able to interfere with MAPK-dependent signaling cascades, thus inhibiting the synthesis of proinflammatory cytokines, prostaglandins, and reactive oxygen species by leukocytes, and adversely affect the migration of myeloid and lymphoid cells. Flavonoid compounds of medicinal plants also inhibit NFκB signaling pathways, activate PPAR transcription factors involved in the synthesis of anti-inflammatory mediators, prevent the formation of synapses between cells of the immune system through inhibition of leukocyte synthesis of molecules of intercellular adhesion. Thus, activation of transcription factors, such as NF-κB, ERK, and STAT3 involved in the proinflammatory immune response, is inhibited by plant stilbene and terpenoids [123].

The majority of studies on the molecular basis of the effect of phytopreparations on immune reactivity relates

to the immunomodulatory action of plant polyphenolic compounds in their composition. Polyphenols are well-known, pharmacologically active compounds with immunomodulatory activity [124]. This category includes flavonoids, phenolic acids and stilbenoids, which are universally formed in plants and exist as free aglycones (non-carbohydrate glycoside fragments) or in the esterification state of glucose and other carbohydrates (glycosides) [125]. Absorbed polyphenols are stable in the conditions of gastrointestinal digestion and interact, first and foremost, with the immune system of the intestinal mucosa, initiating both local and systemic immunomodulatory effects [126].

Decades of research into polyphenols have led to several conclusions regarding their effects on immune system function. Each type of polyphenol binds to one or more immune system cell receptors and thus triggers intracellular signaling pathways that ultimately regulate the host immune response. Phytopreparations and dietary supplements which contain plant polyphenols can modulate the immune response by affecting epigenetic mechanisms such as regulatory DNA methylation, histone modification, and microRNA-mediated posttranscriptional repression that alters the expression of genes encoding key immune factors [127].

Immune system cells express a number of polyphenolic receptors. For example, epigallocatechingallate (EGCG), which is found in large quantities in different varieties of tea, in apples, plums, etc., can interact with three different cellular receptors: the 67 kDa laminin receptor (67LR), associaited with 70 kDa protein chain (ZAP-70) and with RIG-I cytosolic pattern recognition sensor [128, 129]. Of these, 67LR is expressed by neutrophils, monocytes / macrophages [130, 131], mast cells and T cells [132, 133] and regulates the adhesion and inflammatory responses of these cells. RIG-I downstream signaling pathways trigger interferon synthesis [134]. Toll-like receptor (TLR) 4, antigenic T-cell receptor (TCR) $\alpha\beta$, and IgM- (sIgM-) B-cell receptor are receptors for baicalin (a flavone glycoside, contained in large amount in *Scutellaria* plants) on T and B cells. By regulating these receptors, baikalin may affect innate and adaptive immunity responses [135]. In studies with laboratory animals, daidzein and a few other phytoestrogens have been shown to modulate immune cell function by interacting with estrogen membrane and intracellular receptors [136].

Polyphenolic compounds can suppress the dendritic cell (DC) function under conditions of their inflammatory activation. In particular, daidzein (isoflavone contained in soybeans, cereals, and certain medicinal plants), silibinin (flavono-lignan of milk thistle), fisetin (flavonol), epigenin and baikalin can inhibit functional maturation of DC, stimulated by bacterial lipopolysaccharide (LPS): decreasing the expression of histocompatibility molecules of class II and costimulatory molecules [137, 138]. Inhibition of the proinflammatory activation of DC is also characteristic of curcumin and some other phytophenols [139]. The inhibitory effect of phytophenols on the proinflammatory activation of DC is inhibition of the adaptive Th1 immune response. Plant polyphenols, such as daidzein, enotelin B (polyphenol isolated from fireweed and other medicinal plants), activate the functions of $\gamma\delta$T cells and natural killer cells, enhancing IFN-γ synthesis and increasing the expression level of intercellular CD69 molecules (CD25, CD69) [140, 141]. Alcoholic extracts of plants of the milkweed family with high content of biflavonoids enhance the production of antibodies by B cells *in vitro* and *in vivo* [142]. A similar effect was reported for quercetin and its derivatives.

The differentiation of naive T cells and their production of cytokines can be enhanced by numerous phytophenolic compounds. In particular, plant flavones, catechins and flavonones inhibit the synthesis of cytokines involved in the activation of isotype switching of B lymphocytes to IgE synthesis and thus have the ability to suppress allergic inflammatory responses [143, 144]. Contact hypersensitivity reactions are inhibited by the same mechanism by phytoflavones of *Artemisia vestita*, ginkgo, and many other medicinal plants. It should be noted that phytophenols have a general ability to induce a shift of the cytokine profile in serum and other biological fluids from the Th1 profile to the Th2 profile, which is characterized by the activation of humoral immunity reactions, inhibition of inflammatory reactions and activation of reparative processes [145, 146]. Due to this immunomodulatory action, phytophenols activate isotype switching of B cells to IgG and IgM synthesis while inhibiting the synthesis of immediate-type allergic reagins, IgE and IgA. Changes in the local and systemic cytokine profile due to the action of plant polyphenols are characterized by a decrease in IL-1β, IL-6 and TNF-α levels, which are a triad of major cytokines that initiate, support and enhance

inflammation, as well as the synthesis of IL-17, one of the major mediators of autoimmune inflammation. As a rule, the synthesis of IL-4 is enhanced, which is involved in the regulation of antibody production by B-cells [147–149]. It should be noted that phytophenols also have a bimodal dose-dependent modulatory effect on the synthesis of some cytokines. For example, the synthesis of IL-2 that regulates T-cell proliferation can both be enhanced and inhibited by the action of plant phenolic compounds. A peculiarity of the stimulatory effect of phytophenols on the synthesis of this cytokine is the simultaneous enhancement of differentiation of helper type 2 T cells, which inhibit the inflammatory responses of adaptive immunity. The bimodal modulatory effect of phytophenols has also been reported in relation to the synthesis of IL-12, a cytokine whose main source is macrophages, and with a function to stimulate Th1-immune responses. The synthesis of this cytokine by non-sensitized intact macrophages is slightly enhanced in the presence of phytophenols. However, treatment of activated LPS macrophages by phytophenol compounds causes inhibition of their production of IL-12 [150, 151].

The inhibition of inflammation by phytophenols is also achieved by activating differentiation of T-regulatory cells and enhancing their synthesis of immunoregulatory cytokines [152].

Plant polyphenols have the most pronounced modulatory effect on the function of mono- and polymorphonuclear phagocytes (macrophages and neutrophils, respectively). Phytophenols mainly affect MAPK-dependent and NFκB-dependent signaling of these cells. The consequence of this effect is a shift of phagocyte metabolism toward an anti-inflammatory phenotype with synthesis of immunoregulatory cytokines, a decrease in the production of inflammatory metabolites (reactive oxygen and nitrogen forms, eicosanoids, phagolysosome components and enzymes in the cytoplasmic granules of neutrophils). The restorative and reparative processes in tissues are enhanced. That metabolic polarization of phagocytes also has another consequence: inhibitory effect on the inflammatory responses of adaptive immunity effectors, Th1 helper cells [153–155]. These effects are characteristic for phytophenols of plants of the genus *Acanthaceae, Euphorbiacea, Clusiaceae*, and some others.

Perspectives of using phytopreparations in treatment of diseases of hepatobiliary system

The dominant paradigm in the development of medicinal preparations is the concept of constructing optimally selective ligands to influence individual therapeutic targets. However, advances in systemic biology have convincingly shown that selective compounds exhibit less clinical efficacy than multifunctional preparations. Hence, a new approach to the development of medicines occurred, and a one-drug-one-disease treatment strategy is increasingly replaced by the use of combination therapy with several active substances. Such a change in priorities is partly due to the limited therapeutic efficacy of mono-component treatment in the treatment of polyetiological diseases with complex pathophysiology, including HBD. Another reason is the formation of drug resistance to the factors of single-component therapy, as well as the side effects of synthetic monopreparations [41, 42]. In addition, the development of analytical chemistry and molecular biology techniques has broadened our understanding of the therapeutic targets of many diseases and multicomponent therapeutic approaches. Advances in these fields of science form the basis for the following paradigm in drug development: network pharmacology, an interdisciplinary science based on pharmacology, network biology, systems biology, bioinformatics, and other related scientific disciplines. Network pharmacology is aimed at understanding the network interactions between a living organism and the preparations that affect its normal and abnormal functions. This scientific approach aims to use the pharmacological mechanism of action of a medicinal product in a biological network with well-defined therapeutic targets and to enhance the therapeutic efficacy of the drug [156–158].

The scientific principles of network pharmacology are also used in PT, in particular, to create an evidence base on the efficacy of Traditional Chinese Medicine [159, 160]. Phytotherapeutic medical systems in many cases use multicomponent herbal remedies, because numerous studies have proved their higher efficacy compared to the use of individual medicinal plants due to the multi-purpose, synergistic and additive effects of phytoconstituents [43, 44]. Synergy, by definition, is the interaction of two or more agents to produce a combined effect that exceeds the sum of the individual effects of the individual components [161]. Spinella et al. (2002) proposed the classification of synergies into two categories: pharmacodynamic and pharmacokinetic

[162]. In the first case, two or more agents act on the same receptor structures or biological targets, which increases the effect compared to the action of the individual components. Pharmacokinetic synergy happens if the components of a complex preparation interact during the pharmacokinetic processes: absorption, distribution, metabolism of elimination etc. Unlike a synergistic effect, which is the sum of the action of two or more components that exceed their effect on self-administration, an additive effect is a set of effects of components of a combined preparation that do not interact and do not affect the effects of each other [163, 164]. Literature data indicate the synergistic effect of phytochemical components of multicomponent phytoteas [165], synergistic and additive effect of combined extracts of medicinal plants and their essential oils with antibacterial and antiviral effects [166, 167], synergistic anti-inflammatory effect of combined phytochemicals [167, 168]. The future is undoubtedly in the use of therapeutic agents based on medicinal plants for the treatment of HBD by multicomponent herbal remedies. Particular attention should be paid to the introduction of medicinal plants with immunomodulatory properties into the composition of such preparations for directed effect on the immune system, which is one of the integral physiological systems with protective and regulatory effects. An important question is the principle of the arrangement of medicinal plants in the composition of multicomponent herbal preparations. To date, the choice of components of complex phytopreparations is based mainly on knowledge of the biological action of individual medicinal plants. At the same time, a new scientific direction in phytomedicine is being developed, known as phytomix (metabolome analysis for each of the components of the complex phytopreparation, taken separately and in combination with other components, along with the analysis of the correlative relationship between the phytome composition and the desired effect on the biological target) [169, 170]. Phytomix allows evolving from the empirical approach to polyherbal compositions to a scientifically sound creation of complex phytopreparations. To date, several mechanisms of synergistic action of complex phytopreparations have been deciphered: activation or inhibition of signaling by the same receptors; regulation of enzymes and transporters involved in liver and intestinal metabolism to influence the bioavailability of plant BAC; complex influence on factors of formation of drug resistance of target cells; neutralization of side effects of some BAC by the action of others, etc. [171]. Investigation of the synergistic effects of polyherbal compositions will not only facilitate the creation of new complex phytopreparations, but will also reveal the negative synergism between BAC from different medicinal plants and thereby achieve their maximum therapeutic efficacy.

Thus, herbal remedies have been and remain effective, safe and, therefore, promising drugs for the treatment of diseases of the hepatobiliary system. Most promising approach for the development phytoremedies for the treatment of liver and biliary ailments is the use polyherbal formulations combining hepatoprotective and immunomodulatory potentials. Nevertheless, it is necessary to point that current use of herbal medicines in the complementary and altrnative treatment of hepatobiliary disorders is mostly rooted in experience and observation. Metodological approaches of modern evidence-based phytotherapy are needed to increase and proof of efficacy and safety of hepatoprotective and immunomodulatory phytoremedies.

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ЗАСТОСУВАННЯ ФІТОПРЕПАРАТІВ У ЛІКУВАННІ ПАТОЛОГІЇ ГЕПАТОБІЛІАРНОЇ СИСТЕМИ: ТЕНДЕНЦІЇ ТА ПЕРСПЕКТИВИ

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Захворювання органів гепатобіліарної системи становлять важливу медико-соціальну проблему у зв'язку з дедалі зростаючими показниками морбідності в усьому світі. Хвороби печінки та біліарної системи характеризуються комплексною патофізіологією і можуть супроводжуватися розвитком супровідних патологічних станів. Їх лікування потребує застосування багатоцільових препаратів, біологічна дія яких спрямована на різні терапевтичні мішені. Ефективність лікарських засобів для терапії розладів гепатобіліарної системи на сьогодні є низькою, а частота побічних ефектів — достатньо високою. Це актуалізує пошук і розроблення високоефективних гепатопротекторів з низькою частотою побічних ефектів. Джерелом таких препаратів можуть бути лікарські рослини. В огляді узагальнено дані стосовно механізмів гепатопротекторної та імуномодуляторної дії лікарських рослин та їхніх фітоконституєнтів. Окреслено перспективи розробки та застосування фітопрепаратів у лікуванні захворювань органів гепатобіліарної системи.

Ключові слова: захворювання органів гепатобіліарної системи, лікарські рослини, гепатопротектори, імуномодулятори.

ПРИМЕНЕНИЕ ФИТОПРЕПАРАТОВ В ЛЕЧЕНИИ ПАТОЛОГИИ ГЕПАТОБИЛИАРНОЙ СИСТЕМЫ: ТЕНДЕНЦИИ И ПЕРСПЕКТИВЫ

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Заболевания органов гепатобилиарной системы представляют важную медико-социальную проблему в связи с возрастающими показателями морбидности во всем мире. Болезни печени и билиарной системы характеризуются комплексной патофизиологией и могут сопровождаться развитием сопутствующих патологических состояний. Лечение таких заболеваний требует применения многоцелевых препаратов, биологическое действие которых направлено на различные терапевтические мишени. Эффективность существующих на сегодняшний день лекарственных средств для терапии расстройств гепатобилиарной системы остается низкой, а частота побочных эффектов — достаточно высокой. Это актуализирует поиск и разработку высокоэффективных гепатопротекторов с низкой частотой побочных эффектов. Источником таких препаратов могут быть лекарственные растения. В обзоре обобщены данные, касающиеся механизмов гепатопротекторного и иммуномодулирующего действия лекарственных растений и их фитоконституэнтов. Очерчены перспективы разработки и применения фитопрепаратов в лечении заболеваний органов гепатобилиарной системы.

Ключевые слова: заболевания органов гепатобилиарной системы, лекарственные растения, гепатопротекторы, иммуномодуляторы.

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