Pathophysiological association of a functional constipation and metabolic disorders. Perspectives on the pharmacocorrection of digestive system disorders by plant fibers as an example of the use of European plum (Prunus domestica)

Abstract. Background. The search for prokinetics has attracted the attention of medical researchers for several centuries, as impaired motility underlies in the pathogenesis of many diseases, such as gastroesophageal reflux disease, hepatitis, gastric ulcer, irritable bowel syndrome, cancer, etc. The purpose of the study was to study in depth the correlation mechanisms of constipation and other pathologies of the digestive system, as well as ways to implement the pharmacocorrection of these disorders in the conditions of use of vegetable fibers on the example of European plum fruit. Materials and methods. The authors used the following research methods: information-analytical, bibliosemantic, systems approach, structural-logical analysis and comparative content analysis. Results. The analysis of patients for functional constipation is presented, the urgency of the problem of violations of the motor-evacuation function of the intestine and the need to search for new phytobjects for pharmacocorrection of this pathology are formulated. According to the analysis of literary sources, an important direction of scientific developments was described, aimed at studying the pathophysiological association of chronic constipation and metabolic disorders. In our work were given etiological factors of the occurrence of functional constipation against the background of damage to the hepatic parenchyma and pancreatic tissue. Some possible mechanisms for correlation of gastrointestinal, liver, pancreas and skin disorders are presented. The analysis of the pharmaceutical market of Ukraine on the availability of medicines based on plum showed a limited selection of combined preparations and the absence of monocomponent drugs with a laxative effect, which contain the studied plant raw materials. In the work were given facts from the literature on experimental studies of European plum in patients with chronic constipation, as well as the results of studies on models of liver damage. Also, were presented literature data on the phytoclinical characteristics of European plum fruits and the relationship of some biologically active compounds with pharmacological properties. Based on the analysis of literary sources, it was found that European plum is widely distributed and adapted to growing conditions in Ukraine, which indicates a sufficient raw material base and the possibility of using fruits in medical and pharmaceutical practice. Conclusions. According to epidemiological studies and literature analysis, a fairly clear correlation has been found between chronic functional obstruction and a number of metabolic pathologies, the most common of which are liver lesions and pancreas. Some possible mechanisms of correlation of gastrointestinal and liver disorders are presented. Here are some facts from the literature on experimental studies of European plum in patients with chronic constipation and liver damage. Literary data on the prospect of using this raw material in the development of new laxatives with hepatoprotective properties are presented.

Key words: review; functional constipation; intestines; liver; pancreas; skin; plant fibers, European plum fruit

The search for a drugs that normalize the motor-evacuation function of the digestive tract (prokinetics) has attracted the attention of medical researchers for several centuries (Strahl, 1851), as impaired motility underlies the pathogenesis of many diseases, such as gastroesophageal reflux disease, irritable bowel syndrome (IBS), cancer, etc. [1; 2]. IBS, which may manifest in the form of functional constipation, remains an urgent problem in modern medicine. IBS has a significant negative impact on many people’s quality of life and social function. Moreover, it is now known that it can be combined with the development of serious diseases and cause mortality. IBS necessitates a significant increase in health care costs – direct (due to IBS and its related...
Constipation is not a nosological form of the disease or a separate symptom. It is a polyetiological, multifactorial symptom complex of general and gastrointestinal disorders. It is therefore evident that in recent years there has been a steady increase in the incidence of constipation in patients of all ages. They are diagnosed in 30-50% of the adult population and 3% of children who visit a doctor. And in the presence of chronic diseases of the digestive system - in 10-25% of patients [5].

According to official data of the Ministry of Health of Ukraine in 2017, the number of first reported cases of diseases with bowel function disorders was registered over 1 million times, among them 60% were detected in women [6].

The issues of pathogenesis and correction of constipation are of considerable scientific and practical interest, which has been reflected in many contemporary publications [7,8] and in internationally agreed papers: the Roman II, III, IV (1999, 2006, 2016) consensus, WGO. Practice Guideline: Constipation (OMGE2005; WCOG2017, WCOG2019).

Chronic constipation occupies the first place in the structure of gastroenterological and general therapeutic pathology. It should be noted that equally important is that according to epidemiological studies, there is a fairly clear correlation between chronic functional obstruction and a number of metabolic pathologies, the most common of which are liver damage (in particular, non-alcoholic fatty liver disease), development of liver disease, obesity and others.

In the vast majority of patients with functional constipation there is a concomitant multiorgan gastroenterological pathology, that is, not one separate digestive organ is involved in the pathological process, but also related ones - pancreas, intestines, liver and others. This is due to the structural-functional features and the commonality of neurohumoral and endocrine regulation of the digestive system [9].

The pathophysiological relationship between chronic constipation and liver damage is multicomponent, however, one of the trigger causes is the formation of disorders of the qualitative and quantitative composition of the intestinal microflora in patients with constipation. The basis of the latter is quite obvious, given the delay in the transit of intestinal contents and the creation of prerequisites for the active propagation of putrefactive bacteria [10]. The consequence is the active production of proinflammatory molecules (including in hepatocytes) should be considered as a protective reaction of the body to reduce the effects of endotoxins. Thus, the relationship between chronic constipation, bacterial overgrowth, and endotoxin production and liver damage with subsequent fibrosis formation becomes apparent [16].

Normally, cholesterol (CR), which is synthesized in the body, is commonly used to synthesize a number of compounds of steroidal nature - steroid hormones, bile acids, vitamin D, and used as a structural component of cell membranes. The synthesis of bile acids takes place in the liver from CR, after which their conjugated forms of bile enter the intestine through the bile duct and are used in the enteral stage of lipid metabolism. In the small intestine, some of the bile acids, which are subsequently used to transport long-chain fatty acids (as part of cholines complexes) through the membranes of enterocytes, are deconjugated. Due to the enterohepatic circulation absorbed bile acids are again supplied to the liver, some of the unab sorbed bile acids are excreted in the feces. Dysbiosis, under the influence of microflora, significantly activates the deconjugation of bile acids, which are almost completely reabsorbed and reach the liver. This, in turn, suppresses the synthesis of bile acids de novo, and therefore also inhibits the use of cholesterol for the synthesis of bile acids. Cholesterol begins to accumulate in the liver, as functional disorders of hepatocytes make it impossible to synthesize an adequate amount of very low density lipoproteins, which are the main transport form for endogenous lipids. In addition, impaired reticuloendothelial system and inhibition of antioxidant protection is accompanied by activation of lipid peroxidation (LPO) and oxidative modification of blood lipoproteins, which is an important pathogenetic step in the formation of atherosclerosis plaque. Due to the violation of the qualitative and quantitative composition of the intestinal microflora, which develops against the background of chronic constipation, a kind of "vicious circle" is formed (Fig. 1) [11]. Thus, with chronic constipation, there is a decrease in motor-evacuation function of the intestine, resulting in excessive bacterial growth, which, in
turn, leads to endotoxin hyperproduction and increased intestinal wall permeability for microbial components that activate Toll-like receptors cytokines which stimulate synthesis of proinflammatory cytokines. In addition, dysbiotic changes lead to impaired enterohepatic circulation of bile acids, which is accompanied by pathological changes in lipid metabolism and the creation of prerequisites for morphofunctional changes in hepatocytes, in particular - the formation of steatohepatitis and fibrosis [17].

Also important is the activation of oxidative stress, which contributes to the progression of all components of the pathogenesis of combined pathology. That is why, for effective pharmacological correction of chronic functional constipation, it should be considered not as isolated pathology, but as a component of joint pathology, which in particular includes liver lesions, which in turn include disorders of lipid metabolism and activation of oxidative stress [17]. In accordance, pharmacological approaches should include drugs that are capable of the most targeted effect on these components. It should be noted that the use of synthetic drugs is not always appropriate because they are able to activate the processes of microsomal, and therefore free radical oxidation during biotransformation in the liver, which will be accompanied by the progress of oxidative stress. In addition, the features of their pharmacodynamics are directed, mainly, at elimination of constipation as a symptom, without influence on concomitant pathologies [18, 19].

In the case of combined pathologies, priority should be given to herbal remedies that, due to their complex chemical composition, are capable of positively influencing chronic constipation and the course of comorbidities, in particular, liver lesions. In this case, herbal remedies practically do not activate free radical processes, and unlike synthetic drugs, have antioxidant and antiradical properties.

Frequent reasons of constipation are pathological processes that occur in the pancreas. The pancreas is actively involved in the process of digestion of food, often with its inflammation (pancreatitis), the work of the entire GIT is disrupted. It is for this reason that constipation in pancreatitis is a fairly common problem among people suffering from this pathology [20, 21].

The pancreas is part of the digestive system. Its main function is the synthesis and secretion of the hormone insulin, which is responsible for metabolic processes in tissues. If the body begins to experience a deficiency in it, the process of splitting and absorption of nutrients is disrupted, which negatively affects the work of all internal organs and tissues of the body. The main factors that provoke the development of pancreatitis in acute or chronic form are believed to be: alcohol abuse; the presence in the diet a large amount of "heavy" and "harmful" food; stress, lack of sleep; chronic infections. In the case of the development of pancreatitis, the process of slowing down insulin synthesis occurs, the bowel is disrupted, which is the cause of con-

**Fig. 1. The possible pathogenetic relationship of chronic constipation and impaired liver function**
Constipation [22]. As medical practice shows, disorders of the motion are noted in case chronic pancreatitis, as well as in its exacerbation. Constipation in pancreatitis is accompanied by dyskinesia of the colon and bile ducts, which are involved in the process of softening of fecal masses and evacuation from the intestine. Constipation in pancreatitis can also be a manifestation of the development of type II diabetes, which is diagnosed in almost 80% of patients. This is because pancreatitis impairs the synthesis of insulin, which initiates transport to glucose cells and its intracellular metabolism. In normal physiological condition, the pancreas secretes digestive enzymes that provide enteral metabolism of carbohydrates, lipids, and proteins. In the case of pancreatitis, there is a deficiency of enzymes and consequently a violation of the depolymerization (hydrolysis) of food polymers develops [23]. Therefore, most patients with pancreatitis have changes in the motion. In chronic constipation, patients often experience weight loss and excessive irritability. Other symptoms may also occur, such as frequent migraine attacks or dermatitis [22]. The above-mentioned signs of intoxication are due to the fact that in the case of disorders of the intestine, its content is a substrate environment for the action of enzymes of microorganisms, initiating the processes of decay and as a consequence of the formation of toxic products, such as cadaverine, putrescine, indole, scatol, hydaphenogen, mercapto cresol, benzoic acid [23]. Toxicity can be manifested differently, up to loss of consciousness. Moreover, diseases such as cholecystitis and gastritis often develop on the background of inflammation of the pancreas. They are also characterized by frequent constipation. However, cholecystitis and gastritis also have their characteristic symptoms - fever, nausea, vomiting, dizziness, pain in the right hypochondrium, etc. If a person still manages to defecate, the appearance of evacuation of undigested food in the feces attracts attention, which indicates a clear disruption of the pancreas and there are high risks of complications. In this case, severe cutting pain may occur throughout the abdomen at the time when urge to emptying occurs, as well as the change in the color of the evacuation to a pale hue and the appearance of a very unpleasant odor [22]. In addition, the body tries to get rid of these intoxicants, and the antitoxic system of liver hepatocytes does not have time to inactivate them, so they can be excreted through the skin. This causes skin problems. In case of diseases of the organs of GIT the negative changes occur on the skin of the face: dulling of the skin; expansion of pores, which leads to the appearance of “black dots”; the spread of infection in the body provokes the formation of acne; red spots appear; the skin becomes dry; scars occur at the site of inflammation [24, 25, 26].

Antibiotic treatment, malnutrition, chronic constipation and stress can cause systemic dysbiosis (disturbance of normal intestinal microflora). In this state, the body increases the concentration of toxins - products of vital activity of pathogens. In the normal state, our body has three organs through which the excretion of toxic metabolic products occurs - the intestines, kidneys and skin. Nevertheless, the function of the intestine against the background of dysbiosis is impaired, the kidneys can filter and excrete only part of the molecules of a certain molecular weight, and the skin has a heavy load on the excretion of metabolic products. Problematic skin is associated with intestinal dysbiosis (not including diseases such as chronic kidney and liver failure and diabetes). One of the most effective treatments for dysbiosis is the use of prebiotics [27]. Effective prebiotics include a group of plant compounds - cellulose, which is represented by homo- or heteropolysaccharides. Literary and experimental data prove sufficient effective effect on the pharmacocorrection of functional constipation with disorders of the functional state of the liver of vegetable raw materials - fruits of European plum.

According to epidemiological studies on the use of laxatives of herbal origin, patients’ compliance is higher, due to the lower incidence of unwanted side effects and a subjectively higher level of trust in natural origin products. However, the problem of organoleptic qualities (unpleasant taste) of laxatives of vegetable origin (according to the results of the patient survey) remains unresolved; inconvenience arising from their use (problematic use when traveling, medications mostly in liquid form, etc.) and unwanted side effects (flatulence, bloating, and in rare cases - shortness of breath). Accordingly, the high prevalence of chronic constipation, despite the wide arsenal of laxatives, indicates the prospects for the creation of new drugs with these properties. It should be noted that among existing drugs, it is herbal remedies that are characterized by the maximum compliance of patients. Thus, there is a need to develop laxatives of natural origin with pleasant taste qualities and in a convenient form. European plum (Prunus domestica), plum juice and prunes have traditionally been used in folk medicine for hundreds of years to eliminate constipation, but their use in medicine as a drug has hardly been studied [28].

European plum is the most productive of stone fruit crops and most adapted to the soil and climatic conditions of Ukraine, so it is widespread. Traditionally, its consumption does not exceed 6 weeks per year, whereas in economically more developed countries it lasts for a whole year, which proves the sufficiency of raw materials (world plum collection is 1.5 kg per person per year) [29]. The pharmacological properties of European plum are quite diverse and depend on the type of raw material. Yes, its leaves are used in the form of infusion (1:10) for rinsing the mouth with stomatitis due to the pronounced wound healing and anti-inflammatory action (for the same purpose use the leaves fresh or dried in the composition of tea). In addition, the infusion of plum leaves is used for inflammation of the kidneys and bladder, as well as for dermatoses. Another type of raw material - plum bark - exhibits antipyretic, diuretic and anti-inflammatory properties and is used in diarrhea, malaria, prostate adenoma, erysipelas, and other conditions. But the most widely used in folk medicine are plum fruits, which have mild laxative and diuretic effects, have a beneficial effect on metabolism, regulate intestinal peristalsis and metabolism. They are consumed both fresh and in the form of juice and infusion with gastric rings and bloating, constipation,
impaired renal function, liver diseases, various inflammatory diseases of the skin, etc. [30]. Today, the pharmaceutical industry produces complex dietary supplements, of which plum is a component [29, 31]. Dietary supplements include fruits and plum juice, which are combined as a complex with other plant raw materials to produce certain pharmacological properties, including diuretic, laxative, metabolism, etc. The main advantage as manufacturers note is the softness of these medicines. Monocompounds, which as an active substance would include only plums, are absent. Regarding the form of dietary supplements, it should be noted that of the 8 agents 4 have a powder dosage form, 2 - encapsulated, and one representative made in the form of liquid extract and one as gel. Regarding the medicines registered in Ukraine, which include plum, all 4 drugs contain plum extract as active substance. In the described drugs, the raw material is "African plum", namely, the bark. "African plum" bark extract has anti-inflammatory effect on the prostate tissue and enhances its secretory activity, prevents the formation of tumour tissue, eliminates functional disorders of the urinary tract in the adenoma of the prostate gland. Therefore, the primary indication for the use of these drugs is prostate adenoma. All medicines are presented in solid dosage forms: 2 preparations in capsule form and 1 in tablet form. That is, preparations based on European plum fruits are not available in the pharmaceutical market of Ukraine. In the pharmaceutical market of Ukraine, plum based preparations are presented with biologically active additives, which include fruits and juice of European plum. Medicines registered in Ukraine contain as an active substance an extract of African Plum bark and have a capsule and tablet as dosage form [29].

Phytochemical studies of Prunus domestica indicate that the fibers are composed mainly (80 %) of a soluble fraction, including pectin, hemicellulose, cellulose and lignin. The basic simple sugars are sorbitol, fructose and disaccharide - sucrose. Plum fruits contain a considerable amount of organic acids, in particular malic (predominantly quantitative), citric, succinic, benzoic and boric [32, 33]. It should be noted separately, that European plum fruits and prunes contain a significant amount of phenolic compounds (282—922 mg / 100 g fruits) and are represented mainly by chlorogenic, neochlorogenic, coffee, coumaric acids; rutin and proanthocyanidin [34]. The high content of polyphenols is known to cause clear antioxidant and antiradical properties. In addition, the drying of the fruit is accompanied without the participation of enzymes, with the formation of reaction products - melanodins, which show more pronounced antioxidant properties.

There are isolated comparative clinical trials using European plum in chronic constipation in the scientific literature. A prospective randomized controlled clinical trial, published by Attaluri et al. compared the effectiveness and tolerance of prunes and plantain seed shells in adults patients with chronic constipation. Study participants (age 18-75 years, mean age - 38 years) received either prunes (50 g per day, fiber = 6 g / day) or plantain (11 g per day, fiber = 6 g / day) for 3 weeks with a one-week "laundering" period. The study evaluated the following criteria: daily symptoms; number of defecation acts; number of bowel movements with subjective complete bowel emptying per week; elimination of constipation symptoms; evacuation consistency; the need to exercise during the act of defecation; tolerance of prunes and plantain seed shells; taste qualities. According to the study, the number of defecation acts increased significantly in the group of patients receiving prunes (p <0.05), compared with the group of patients receiving plantain. There was a significant improvement in the coherence of tenesmus and bowel movements in the plum treated group compared to the plantain seed shells. Constipation symptoms and the need for exertion during the act of defecation did not differ significantly in the two study groups. The tolerance of the prunes and the plantain was comparable and no adverse side effects associated with their use were noted during application. The authors noted that, by critically evaluating all study criteria, dried plum fruits were more effective than the plantain seed coat. Given the equally good tolerability, but the higher taste of the plum, the dried plum fruits should be considered as the first line of therapy for chronic constipation in adult patients [28].

Separate studies of the laxative properties of the plum indicate that the laxative effect is realized due to the content of oxyphenisatine, which interacts directly with the receptors on the membrane of enterocytes and acts as a contact laxative. The high content of plum fruits of sorbitol and chlorogenic acid contributes to the realization of the laxative effect, but already by increasing the osmotic pressure (proven for sorbitol action). In addition, the high content of chlorogenic acid causes the pronounced antioxidant properties and normalization of carbohydrate and lipid metabolism, which are usually disrupted in patients with chronic constipation [35].

In a randomized double-blind crossover study, the effectiveness of adding yogurt (260 g per day) containing galactooligosaccharides (12 g per day), prunes (12 g per day) and flax seeds (12 g per day) was studied. Decreased symptoms of constipation have been shown in elderly patients with mild constipation. In the study of the pharmacological properties of plum juice, in addition to the alleged laxative effect, the activity of marker liver enzymes, in particular, alanine aminotransferase (ALT) and alkaline phosphatase (ALP) in serum, indicating the prospect of using European plum in patients with chronic constipation and concomitant liver lesions [36]. The methanol-ethanol (70:30) extract from Prunus domestica was investigated in experimental liver lesions induced by paracetamol and tetrachloromethane in rats. Hepatotoxic agents were administered at doses of 2 g/kg (paracetamol) and 1.5 ml / kg (tetrachloromethane), which was accompanied by the development of marked liver function abnormalities and was confirmed by the dynamics of biochemical markers: a significant increase in ALT activity, aspartate aminotransferase, total and direct bilirubin and reduced levels of reducing glutathione (RGSH), superoxide dismutase (SOD) and catalase activity in liver tissue, as well as the activation of LPO. The use of extracts of European plums at doses of 150 mg / kg and 300 mg / kg
was accompanied by the normalization of all these markers, which the authors associate with the pronounced antioxidant activity of the extracts, since the hepatotoxic effect of paracetamol and tetrachloromethane is realized first by oxidation. The antioxidant properties of plums are due to the high content of polyphenolic compounds, as well as vitamins that exhibit antioxidant properties, in particular ascorbic acid, tocopherol and rutin. Thus, the extract from Prunus domestica showed distinct hepatoprotective properties against the background of the introduction of toxic to liver tissue compounds, which indicates the prospect of its use as a hepatoprotective agent [37].

It is important to note that owing to the multicomponent chemical composition, plum fruits exhibit different types of pharmacological activity (except for laxatives and antioxidants mentioned above).

The ethanol fraction of plum juice has been shown to be able to induce apoptotic changes in human colon carcinoma cells. This is extremely important in the aspect of creating a laxative based on plums, since it is known that chronic constipation is a prognostic criterion for the development of colon cancer [38].

Hepatitis C virus (HCV) is one of the major causes of a chronic liver damage that further requires transplantation. Standard treatments are largely limited to frequent cases of development of resistance to therapy, severe adverse reactions, lack of response to therapy, etc. That is why the development and research of new drugs for the treatment of HCV-associated diseases is a pressing issue. Bose et al. investigated the influence of flavonoid rutin isolated from European plum (Prunus domestica) fruits as an inhibitor of HCV penetration into cells. The authors found that the plum routine significantly inhibited the binding of HCV-like particles to hepatoma cells and inhibited the entry of the virus into cells. In this case, the routine was found to be non-toxic to hepatoma cells, affecting only the early stages of HCV life cycle. Thus, the study of the routine isolated from Prunus domestica is promising in the aspect of developing drugs for the treatment of HCV-associated liver pathologies [39].

In a number of preclinical studies, prunes have demonstrated its ability to normalize lipid metabolism disorders, in particular by lowering cholesterol, low-density lipoproteins, reducing serum and hepatic cholesterol levels in rats with hyperlipidaemia. In addition, in vitro fruit plums have the ability to bind excess bile acids (activity is 50 % of cholestyramine binding capacity). The latter is also extremely important for patients with chronic constipation, in which the enterohepatic circulation of bile acids is impaired [36].

The coffee acid contained in the plum fruits reduced the level of reactive oxygen species in smooth muscle cells, which were caused by the action of angiotensin II, blood vessels in hypertensive rats. This indicates the potential ability of the plum fruit to prevent the progression of vascular damage in hypertension. In preclinical studies in mice, the anxiolytic effect of chlorogenic acid (20 mg / kg) obtained from plum fruits was confirmed. Anti-anxiety activity was probably realized through the activation of benzodiazepine receptors. It is known that oxidative stress in the brain exacerbates the course of anxiety disorders, and the distinctive antioxidant properties of the plum can offset these disorders. In addition, anxiolytic action is very important in patients with chronic constipation, since one of the ethiopathogenetic causes of constipation is neurologic pathology [40].

Thus, the fruits of European plum (Prunus domestica) is a promising raw material for the creation of a laxative of natural origin, which, in addition to its attenuating properties, has a membrane-stabilizing, anti-inflammatory, prebiotic effect, normalizes various links of lipid metabolism and potentially proactive.

Conclusions

1. According to the analysis of literary sources, an important direction of scientific developments aimed at the pathophysiological association of chronic constipation and metabolic disorders has been described. According to epidemiological studies, a clear correlation has been found between chronic functional obstruction and a number of metabolic pathologies, the most common of which are liver lesions. Some possible mechanisms of correlation of GIT and liver disorders are presented.

2. The conducted analysis of the pharmaceutical market of Ukraine regarding the presence of plum-based drugs showed the limited choice of combination drugs and the absence of monodrugs containing this medicinal plant raw material. The relevance of the choice of direction and object of research is shown.

3. Facts from the literature on experimental studies of European plum in patients with chronic constipation, as well as the results of studies on models of liver damage were described. Particular attention was paid to the use of European plum fruits and the prospect of using the indicated raw material in the development of new drugs - laxative activity with hepatoprotective properties. Based on the analysis of literature sources, it is established that European plum is widely distributed and adapted to the conditions of growth in the territory of Ukraine and indicates the sufficiency of raw materials and the possibility of using fruits in medical and pharmaceutical practice.

Conflicts of interests. Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

References

1. Drinnan M., Powell J., Nikkar-Esfahani A., Hearing R.C., Doyle J. Gastroesophageal and extraesophageal reflux symptoms: Similarities and differences. Laryngoscope. 2013; 125:424-430. doi: 10.1002/lary.24950.

2. Drossman D. A., Hasler W. L. Rome IV - Functional GI Disorders: Disorders of Gut–Brain Interaction. Gastroenterology2016;150(6):1257-1261. doi: 10.1053/j.gastro.2016.03.035.

3. Benninga M. A., Nurko S., Faure C, Hyman E. P., Roberts Ian St. J., Schechter N. L. Childhood Functional Gastro-
intestinal Disorders: Neonate/Toddler. Gastroenterology. 2016; 150(6):1443-1455. doi: 10.1053/j.gastro.2016.02.016.

4. Hai Wei Xin, Xiu Cai Fang, Li Ming Zhu et al. Diagnosis of functional constipation: Agreement between Rome III and Rome II criteria and evaluation for the practicality. J Dig Dis 2014; 15(6):314-320. doi: 10.1111/1751-2980.12145.

5. Quigley E. M., Fried M., Gwee K.A. et al. World Gastroenterology Organisation Global Guidelines Irritable Bowel Syndrome: A Global Perspective Update September 2015. J Clin Gastroenterol. 2016; 50:704-713. doi: 10.1097/MCG.0000000000000653.

6. Заклады здоровья: и Державна служба статистики України. Захворюваність населення України у 2017 році Статистичний збірник. Сайт URL: http://www.ukrstat.gov.ua (дата звернення 22.10.19 р.).

7. Werth B. L., Williams К. A., Pont L. G.A longitudinal study of constipation and laxative use in a community-dwelling elderly population. Arch Gerontol Geriatr. 2015; 60(3):418-24. doi: 10.1016/j.archger.2015.02.004.

8. Li F., Fu T., Tong W., Zhang A., Li C., Gao Y. Effect of Different Surgical Options on Curative Effect, Nutrition, and Health Status of Patients with Slow-Transit Constipation. Int J Colorectal Dis. 2014; 29(12):1551-1556. doi: 10.1007/s00384-014-2014-8.

9. Sharkey K. A., MAwe G. M. Neurohormonal signalling in the gastrointestinal tract: new. J Physiol. 2014; 592(14):2923-2925. doi: 10.1113/jphysiol.2014.275487.

10. Lokiec K., Kluptiska G., Walecka-Kapica E. Estimation of small intestinal bacterial overgrowth in patients with constipation and diarrhea irritable bowel syndrome. Pol. Merkur. Lekarski. 2014; 36(215):307-310.

11. Фоминых Ю. А., Шабров А. В., Успенский Ю. П., Иванов С. В. Функциональный запор у пациентов с метоболическим синдромом. Экспериментальная и клиническая гастроэнтерология. 2017. № 143(7), С. 151-154.

12. Кучериво Ю. А., Мясковская Е. А. Эпидемиологическая и патофизиологическая ассоциация неалкогольного стеатогепатита и функционального запора. Возможно ли избежать полипрагмазии в практике гастроэнтеролога? Гастроэнтерология. 2017. № 1, С. 314-320.

13. Geric G., Maillet V., Paradis V.et.al. Oxidative stress promotes pathologic polypliodization in nonalcoholic fatty liver disease. The Journal of clinical investigation. 2015; 125(3):981-992. doi: 10.1172/JCI73957.

14. Geric G., Maillet V., Paradis V.et.al. Oxidative stress promotes pathologic polypliodization in nonalcoholic fatty liver disease. The Journal of clinical investigation. 2015; 125(3):981-992. doi: 10.1172/JCI73957.

15. Spahis S., Delvin E., Borys J. M., Levy E.et.al. Oxidative stress as a critical factor in nonalcoholic fatty liver disease pathogenesis. Antioxidants & Redox Signaling. 2017; 26(10):519-541. doi: 10.1089/ars.2016.6767.

16. Vajro P., Paolella G., Fasano A. Microbiota and gut-liver axis: their influences on obesity and obesity-related liver disease. J. Pediatr. Gastroenterol. Nutr. 2013;56:461-468. doi: 10.1097/MPG.0b013e3182846bb5.

17. Селевтеров П. В., Синяк С. И., Радченко В. Г. Роль дисбиоза кишечника в развитии митохондриальной дисфункции и неалкогольной жировой болезни печени // Медицинский Совет. 2018. № 6, С. 89-95. doi:10.21518/2079-701X-2018-6-85-95.

18. Tack J., Corsetti M. Prucalopride: evaluation of the pharmacokinetics, pharmacodynamics, efficacy and safety in the treatment of chronic constipation. Exp. Opin. Drug Metab. Toxicol. 2012;8(10):1327-1335. doi: 10.1517/17425255.2012.719497.

19. Del Campo J. A., Gallego P., Grande L. Role of inflammatory responses in liver diseases: Therapeutic strategies. World-journal-of-hepatology. 2018; 10(1):1-7. doi: 10.4254/wjh.v10.i1.1.

20. Иванов Б. В., Гастроэнтрология. Национальное руководство: краткое издание. Москва: ГЭОТАР-Медиа. 2015. С. 480.

21. Барановский А. Ю. Диетология. 4-е изд. Санкт-Петербург: Питер, 2012. С. 1024.

22. Масловский Л. В. Хронический панкреатит. Новые медицинские советы. 2016. № 14, С. 32-35. doi:10.21518/2079-701X-2016-14-32-35.

23. Бюхнін, підручник / за заг.ред. проф. А. Л. Загайка, проф. К. В. Александровой. Харків: Форт, 2014. 728 с.

24. Дерматология, венерология: підручник / за ред. проф. В. І. Степаненко. Києв: КІМ, 2014. С. 41-47.

25. Караулов А. В., Быков С. А., Быков А. С. Иммунология, микробиология и иммунопатологии. Москва: Бином, 2012. 328 с.

26. Konovaleva T. S. Stan mikrobiocenozu kishchenka u xvorih na vuzuveny khvorobu i vlyo vnego poruszena na kli- nicnyj perebir dermatou. Ukrainskij zhurnal dermatologii, venerologii, kozmetologii. 2014; 1(52), С. 41-47.

27. Бабак О. Я., Фаденко Г. Д., Ступник К. А. Роль пробиотических продуктов питания в профилактике и ле- чении функциональных запоров. Сучасна гастроентерологія. 2012. № 5(67), С. 116-119.

28. Attaluri A., Donahoe R., Valestin J., Brown K., Rao S. Randomised clinical trial: dried plums (prunes) vs. psyllium for constipation. Alimentary pharmacy & therapeutics. 2011; 33(7):822-828. doi: 10.1111/j.1365-2036.2011.04594.

29. Лукієнко О. В., Соколова А. Є., Горбашь О. М. Аналіз вітчизняного фармацевтичного ринку препаратів на основі сливи. Фітопаттерна. 2012. № 1, С. 86-89.

30. Тураева Н. И. Лечебные свойства сливы. Биология и интегративная медицина». 2017. № 1, С. 314-320.

31. Нормативно-директивные документы МОЗ Украины. Сайт URL: http://mozdocs.kiev.ua/ (дата звернення 15.11.19 р.).

32. Shaht M. M., Upyr T. V., Shapoval O. M., Lenchyk L. V., Georgiev K. Determination of phenolic compounds in Prunus domestica fruits extract and its pharmacological activity. J of IMAB. 2019; 25(2):2589-2594. doi: https://doi.org/10.5272/jimb.2019252.2589.

33. Спосіб одержання водорозчинного полісахаридного препарату на основі сливи. Биохімія, природовик. 2013. № 1, С. 10-15.
Патофізіологічна асоціація функціонального запору та метаболічних порушень. Перспективи фармакокорекції порушень травної системи рослинними волокнами на прикладі використання плодів сливи домашньої (Prunus domestica)

Резюме. Актуальність. Пошук прокінетиків привертає увагу лікарів-дослідників протягом кількох століть, оскільки порушення моторики лежать в основі патогенезу багатьох захворювань. Пандемія коронавірусної хвороби привела до значного зростання народжуваності і хвороб, зокрема, вагітних з хронічним запором, а також результати досліджень на моделях ураження печінки. Представлені літературні дані щодо фітохімічної характеристики плодів сливи домашньої й можливість використання плодів у медичній і фармацевтичній практиці.

Матеріали та методи. Авторами були витягнуті дані щодо фітохімічної характеристики плодів сливи домашньої з фармакологічними властивостями. На підставі проведеного аналізу літературних джерел встановлено, що слива домашня є потенційно активним фармакологічним ресурсом.

Результати. Представлені аналітичні дані щодо функціонального запору, сформулювана актуальна проблема порушень. Опрацювання наукових досліджень дозволило виявити перспективи використання фармакокорекції порушень травної системи рослинними волокнами на прикладі використання плодів сливи домашньої (Prunus domestica).

Ключові слова: фармакофігуратор, фармакокорекція, хронічний запір, кишечник, фармакологічні властивості, слива домашня, фітоактивні ресурси.

Патофізіологічна асоціація функціонального запору та метаболічних порушень. Перспективи фармакокорекції порушень травної системи рослинними волокнами на прикладі використання плодів сливи домашньої (Prunus domestica)

Резюме. Актуальність. Пошук прокінетиків привертає увагу лікарів-дослідників протягом кількох століть, оскільки порушення моторики лежать в основі патогенезу багатьох захворювань. Пандемія коронавірусної хвороби привела до значного зростання народжуваності і хвороб, зокрема, вагітних з хронічним запором, а також результати досліджень на моделях ураження печінки. Представлені літературні дані щодо фітохімічної характеристики плодів сливи домашньої й можливість використання плодів у медичній і фармацевтичній практиці.

Матеріали та методи. Авторами були витягнуті дані щодо фітохімічної характеристики плодів сливи домашньої з фармакологічними властивостями. На підставі проведеного аналізу літературних джерел встановлено, що слива домашня є потенційно активним фармакологічним ресурсом.

Результати. Представлені аналітичні дані щодо функціонального запору, сформулювана актуальна проблема порушень. Опрацювання наукових досліджень дозволило виявити перспективи використання фармакокорекції порушень травної системи рослинними волокнами на прикладі використання плодів сливи домашньої (Prunus domestica).

Ключові слова: фармакофігуратор, фармакокорекція, хронічний запір, кишечник, фармакологічні властивості, слива домашня, фітоактивні ресурси.

Патофізіологічна асоціація функціонального запору та метаболічних порушень. Перспективи фармакокорекції порушень травної системи рослинними волокнами на прикладі використання плодів сливи домашньої (Prunus domestica)
Материалы и методы. Авторами были использованы следующие методы исследования информационно-аналитический, библиосемантический, системного подхода, структурно-логического анализа и сравнительного контент-анализа. Результаты. Представлен анализ касательно больных функциональным запором, сформулирована актуальность проблемы нарушений моторно-эвакуаторной функции кишечника и необходимость поиска новых фитообъектов для фармакокоррекции указанной патологии. Согласно анализу литературных источников было описано важное направление научных разработок, направленных на изучение патофизиологической ассоциации хронического запора и метаболических нарушений. Приведенные этиологические факторы возникновения функциональных запоров на фоне поражения печеночной паренхимы и тканей поджелудочной железы. Представлены некоторые возможные механизмы корреляции нарушений ЖКТ, печени, поджелудочной железы и кожи. Проведённый анализ фармацевтического рынка Украины о наличии лекарственных средств на основе сливы показал ограниченный выбор комбинированных препаратов и отсутствие монокомпонентных средств со слабительным действием, которые содержат исследуемое растительное сырье. Приведены факты из литературных источников по экспериментальным исследованиям сливы домашней у пациентов с хроническим запором, а также результаты исследований на моделях поражения печени. Представлены литературные данные фитохимической характеристики плодов сливы домашней взаимосвязь некоторых биологически активных соединений с фармакологическими свойствами. На основании проведенного анализа литературных источников установлено, что слива домашняя широко распространена и адаптирована к условиям произрастания на территории Украины и свидетельствует о достаточной сырьевой базе, а также возможностью использования плодов в медицинской и фармацевтической практике. Выводы. Согласно с данными эпидемиологических исследований и анализа литературных источников установлена достаточно четкая корреляция между хронической функциональной обструкцией и рядом метаболических патологий, среди которых наиболее частыми являются поражения печени и поджелудочной железы. Представлены некоторые возможные механизмы корреляции нарушений со стороны ЖКТ и печени. Приведены факты из литературных источников по экспериментальным исследованиям сливы домашней у пациентов с хроническим запором и поражением печени. Представлены литературные данные о перспективах использования указанного сырья в разработке новых слабительных лекарственных средств с гепатопротективными свойствами. Ключевые слова: обзор; функциональный запор; кишечник; печень; поджелудочная железа; кожа; растительные волокна; плоды сливы домашней