THE THEORETICAL SUBSTANTIATION OF THE SEARCH FOR POTENTIAL MEDICINAL PRODUCTS CONTAINING BIOLOGICALLY ACTIVE SUBSTANCES FROM THE FOOD PLANT RAW MATERIAL

Considering that food plants have a stable raw material base and the proven safety to the human body the use of the raw material of food plants to create new medicines is relevant and has several advantages, such as a sufficient raw material base, significant efficiency and high safety level.

**Aim.** To substantiate theoretically the search for potential medicinal products based on the food plant raw material, in particular carrot roots and parsnip roots.

**Materials and methods.** Clinical and pharmacological analysis was conducted using the databases of scientific information (articles, monographs, abstracts of theses, etc.) from Ukraine and worldwide (NCBI, Vernadsky National Library of Ukraine, Google Scholar, Google Academy). This information contains data on the search, development, preclinical studies, clinical trials, application of medicinal products on the basis of the plant raw material, in particular carrot roots and parsnip roots, in official and folk medicine.

**Results.** The study conducted has allowed us to prove the relevance, timeliness, expediency and prospect for searching new promising medicinal products on the basis of the raw material of food plants of the *Apium* genus – carrot and parsnip roots.

**Conclusions.** The study has proven that the plants of the *Apium* genus – carrot and parsnip have a powerful, affordable and cheap raw material base are the sources of substances containing the amount of biologically active substances that are promising for the creation of new medicinal products on their basis with the cytoprotective, anti-inflammatory, nephroprotective, wound healing, reparative action, and they are promising for introduction into medical practice for the treatment of skin lesions.

**Key words:** biologically active substances; substances of plant origin; raw material from plants of *Apium* genus; carrot roots; parsnip roots
Сurrently, it has been proven that products of natural (plant, animal, etc.) origin, although they are sometimes inferior to synthetic products in efficiency, predominate in safety. According to Chekman I. S. et al. (2014) [1] and Morozova T. Ye. et al. (2015) [2] and taking into account polypragmasy, as well as the use of off-label medicines the issue of drug safety is one of the top priorities of modern medicine.

Scientists Shymorova Yu.Ye. et al. think that the share of medicines based on the plant raw material in the structure of the modern pharmaceutical market is increasing steadily [3]. The wide spectrum of their action is explained by the composition of biologically active substances (BAS), the simultaneous presence of compounds of different structures (essential oils, phenols, coumarins, alkaloids, etc.). It is also important that some natural substances do not have synthetic analogs yet. Public demand for medicinal products of natural origin is not fully met due to a shortage of the medicinal plant raw material. Many medicinal plants used in domestic traditional medicine have not formed industrial thickets for long period of time, and some of them are rare or endangered.

Therefore, in order to search and create new medicinal products it is appropriate to select the raw material of food plants. This is due to the fact that food plants have a stable raw material base and proven safety to the human body since they have been applied for food for a long time and in quantities that far exceed the permissible amount in toxicology. Therefore, the use of the raw material of cultivated food plants to create new medicines is relevant and has several advantages, such as a sufficient raw material base, significant efficiency and high safety level.

Taking into account the foregoing the aim of this work is to substantiate theoretically the search for potential natural medicinal products based on the food plant raw material, in particular carrot roots (CR) and parsnip roots (PR).

Materials and methods

To achieve this aim the clinical and pharmacological analysis was conducted using the databases of scientific information from Ukraine and worldwide. The following internet electronic resources were applied as sources of information: National Center for Biotechnology Information (PubMed, MedGen, MEDLINE (Leasing), PubMed Central, BLAST, Nucleotide, Genome, SNP, Gene, Protein, PubChem), V. I. Vernadsky National Library of Ukraine, Google Scholar, Google Academy, and others. The following keywords were used as a search query: carrot roots, parsnip roots, Celery family, ethnopharmacology, folk medicine, traditional medicine, therapeutic effect. The sources of scientific information were analyzed in the form of articles in professional journals of Ukraine and the world, monographs, abstracts of theses, which contained data on the search, development, preclinical studies, clinical trials, application of medicinal products on the basis of the raw material of food plants of the Celery genus – carrot and parsnip roots.

Results and discussion

The study conducted has allowed us to obtain results, which indicate the relevance, timeliness, expediency and prospect for searching new promising medicinal products on the basis of the raw material of food plants of the Celery genus – carrot and parsnip roots.

It has been shown that medicinal plants are used the most widely in official medicine for creating medicinal products of natural origin. According to Garnaya O. V. et al. [4] it is due to the fact that the medicinal plant raw material contains the amount of BAS, which belong to different chemical classes, subclasses, groups, and each group is represented by more than one compound with different degrees of the pharmacological activity. The polyvalence of
The therapeutic effect of medicinal plants is their advantage, whereas for synthetic drugs the most valuable feature is the narrow effect, specificity, selectivity of action.

Herbal medicinal products occupy almost one third of the world market of medicines [5, 6]. Quite often they are special, and it is almost impossible to replace them with synthetic drugs both because of the complexity of the structure, and the fact that the medicinal plant raw material contains a complex system of BAS, which collectively give the biological activity of a particular direction [6]. In most cases, medicinal products based on plants are preferred compared to synthetic drugs of predominantly to the prevention and treatment of early stages of the disease, in chronic course of the disease, as well as in dermatology and cosmetology [7].

Degtiariova K. O., et al. consider that herbal medicinal products are time-proved and applied in medicine for improvement and prevention of human diseases [8]. Since ancient times, people have used plants as the only and most effective method of folk treatment. Currently, herbs are replaced by phytopreparations, which occupy a prominent place in modern pharmacotherapy. Phytopreparations contain substances isolated from plants, purified complexes of natural substances, infusions, decoctions, tinctures, extracts. Pure substances of plant origin, which contain phytopreparations, by their characteristics are fully consistent with synthetic agents. Natural substances containing phytopreparations are close to the human body, from which follow the features, which consideration is necessary in the process of their experimental and clinical research. In addition, herbal medicinal products have low toxicity and a rather high efficiency, a wide range of therapeutic effects, minimum side effects, relatively cheap cost compared to synthetic drugs [8].

Therefore, in order to expand the nomenclature of Ukrainian herbal medicinal products pharmacognosists of the National University of Pharmacy created a dense extract from carrot roots and a dense extract from parsnip roots using the raw material from food plants of the Apium genus, and provided these extracts to the researchers of the Department of Pharmacology and Drug Prescription of the Kharkiv National Medical University for the pharmacological study.

The use of a dense extract as a dosage form is due to the fact that the extracts are one of the oldest dosage forms of traditional medicine [8]. The process of plant material extraction should be considered as a variety of physicochemical processes that take place both inside the cell and on its surface. Along with the dissolution processes there are phenomena of diffusion, osmosis, adsorption, etc. All these processes affect the composition of BAS contained in the extract, and, therefore, their pharmacological properties.

The choice of CR for the purpose of creating a potential medicinal product is due to the specific composition of BAS, which explains the widespread application of CR not only in food as a nutritional culture, but also with the therapeutic purpose in folk medicine [9]. The work of Paziuk D. M. V. et al. [9] contain the data that carrot seed (Daucus carota L. subsp. sativus (Hoffm.) Roehl.) of the Apiaceae family is rich in different classes of BAS, among them there are carotenoids (α-, β-, γ-, ξ-carotin), vitamins (thiamine, riboflavin, niacin, folic acid, vitamin C and E), minerals (potassium, calcium, phosphorus, iron, magnesium, zinc, etc.), pectin substances, volatile and phenolic compounds, etc. [9]. The use of carrots is prescribed for diseases of the cardiovascular system (myocardial infarction, atherosclerosis), urinary tract, in diseases associated with mineral metabolism disorders (poliarthritis, osteochondrosis), for the prevention of some forms of cancer. Carrots are used as an auxiliary therapeutic agent in conjunctivitis, keratitis, blepharitis, for the treatment of chronic skin diseases, purulent wounds, burns, for enhancing the resistance of the body to colds, etc. [9].

The work of Chandra P. et al. [10] confirmed that plants were a valuable basis for the creation of new medicines, and they were considered as an alternative strategy for the search for new drugs. The data shows that in Indo-China carrots are used to regulate the functions of the stomach and intestines. Scientists demonstrated that the extract derived from Daucus carota had analgesic, anti-inflammatory, contraceptive, antitumor, hepatoprotective, antihypertensive, antispasmodic, antibacterial and hypoglycemic properties, inhibited monoamine oxidase and enzyme cyclooxygenase [10, 11].

The research of Sodimbaku V. et al. [12] was aimed at studying the nephroprotective properties of the alcoholic extract from carrot roots under conditions of gentamicin-induced nephropathy in white rats. It was found that intoxication with gentamicin induced a significant (P < 0.01) increase in the urea concentration in the serum, blood urea nitrogen, uric acid and creatinine. In groups receiving the alcoholic extract from carrot roots a dose-dependent decrease in the concentration of these parameters was observed, it was confirmed by histological studies. This indicates a significant dose-dependent nephroprotective effect of the alcoholic extract from carrot roots under conditions of gentamicin-induced nephropathy [12].

In the publication [13] scientists Shebaby W. N. et al. report that their previous studies showed that the oil extract from wild carrots had the antitumor activity in vitro and in vivo. According to the study published the carbohydrate carboxy pentane-diethyl ether fraction (F2) showed the improved selective cytotoxicity against the oncogenic variants of NaCaTa-Ras compared to neoconogenic
HaCaTom of human keratinocytes by inducing caspase-dependent cell death through activation of apoptosis. The antitumor activity of F2 was also confirmed \textit{in vivo} using a DMBA/TPA carcinogenesis model in mice. The data presented show that F2 fraction of pentane-diethyl ether of carrot has a significant anti-tumor activity against DMBA/TPA-induced carcinogenesis of the skin [13].

The aim of the study of Soares G. R. [14] was to assess the preventive potential of the carrot extract against carcinogenesis in the tongue of rats induced by 4-nitroquinoline-1-oxide (4NQO). It was proven that the carrot extract was capable of protecting the tissues of the oral cavity of rats from the damage induced by 4NQO due to the antioxidant, anti-inflammatory, antiproliferative and antimutagenic activity [14].

Scientists Blando F., Calabriso N., Berland H., et al. investigated the \textit{in vivo} biological activity of anthocyanins from different types of the plant raw material, including carrot roots, their effect on human endothelial cells [15]. It was found that anthocyanins reduced the expression of endothelial inflammatory antigens; it indicated their potential positive effect on the cardiovascular protection and anti-inflammatory activity. Their antiradical and antioxidant effects were also proven [15].

Scientists Attiq A. et al. analyzed literary data on the effects of natural medicines on the processes of inflammation [16]. In this work it was shown that the high content of essential oils that were present in the carrot roots was responsible for most of their pharmacological effects. The results of the study in determining the mechanisms of the anti-inflammatory activity of essential oils isolated from carrot roots showed that 2,4,5-trimethoxybenzaldehyde, oleic acid and \textit{trans-}azaron inhibited the activity of COX-2 by 52.69, 68.41 and 64.39 % and did not reveal the significant activity against COX-1 [16].

Parsnip roots have been chosen to obtain a dense extract and further pharmacological studies since parsnip contains the following BAS: fatty oil (0.5 %), essential oils (up to 3.5 %), uronic acids, peptic substances (7.3 %), starch (4 %), carbohydrates (arabinose, galactose, xylose, mannose, rhamnose, sucrose, fructose) (8.6-10.6 %), ascorbic acid (5.40 mg %), nicotine (0.94 mg %) and pantothenic acid (0.5 mg %), riboflavin, thiamine, carotene (0.03 mg %), mineral salts: potassium (342 mg %), phosphorus (69 mg %) [17, 18]. The presence of these BAS in CR leads to the potential for accumulation of sufficient concentrations of biologically active compounds (xanthotoxin, bergapten, imperatorin, psoralen) and be the raw material producer of new medicines for the treatment of skin diseases. It has been shown that the Ukrainian market of dermatological products of plant origin is in acute need of photosensitizing medicinal products. Antimicrobial and fungicidal properties of essential oils of parsnip, which require further detailed study, are also of interest [3].

"Ethnopharmacology of Love" article by Leonti and Laura Casu contains data about the fact that parsnip roots were used in the field of ethnomedicine as aphrodisiacs and for the treatment of erectile dysfunction [19].

Scientists Degerli S. et al. proved that the aqueous extract of parsnip in the dose of 32.00 mg/ml \textit{in vitro} destroyed 40.3 % and 23.0 % of trophozoites and cysts of amoebae, respectively, and exhibited the amebicidal activity [20].

Mahdizadeh S. et al. published the results of the study of "The Canon of Medicine" by Avicenna with the purpose to find anti-inflammatory and analgesic drugs presented in this encyclopedia [21]. The authors provided data that the parsnip raw material were used as an anti-inflammatory and anesthetic agents for oral and topical use for the treatment of headache, fever, dermatitis, stomatitis, conjunctivitis [21].

Palamarchuk O. P. [22] presented the results of a comprehensive study of morphobiological and biochemical characteristics of 6 species of the \textit{Pastinaca L} genus, and their antimicrobial activity was determined.

Taking into account the data mentioned above it was useful to perform the analysis of scientific works of domestic researchers characterizing the current state of searching new medicines in Ukraine, in particular drugs with the reparative action based on the plant raw material, which was promising for the treatment of skin lesions of diverse etiology. Therefore, the domestic databases of scientific in-
formation on the search, creation of medicinal products of plant origin for the treatment of skin lesions and their application in medical practice were studied.

For example, Rekhletska O. V. worked upon the composition, technology and study of phytopreparations from common birch (Betula verrucosa) to treat infectious skin diseases [23]. It was determined that liquid extracts of buds and leaves of common birch and lotions based on them were active against strains of S. aureus, S. epidermidis, Str. faecalis, Candida albicans microorganisms, and their application were microbiologically and toxicologically safe [23].

Scientist Ruban O. A. developed scientific and methodical approach to the development of medical forms based on black currant polysaccharides [24]. The composition and technology of “Glucuronic” ointment on the emulsion basis for the treatment of skin diseases of allergic genesis was developed [24].

Chorna N. A. substantiated theoretically and experimentally the composition and rational formulation of a new homeopathic ointment containing matrix infusions of bee venom and propolis, as well as walnut oil [25]. In the experiment in laboratory animals she proved the promising use of a homeopathic ointment of combined action under the conventional name “Api-derma” for the treatment of allergic contact dermatitis [25].

Kovalyov V. V. substantiated theoretically and experimentally the composition and formulation of a new medicinal product in the form of “Phyiolet” ointment containing plant antisepsics (a dense extract of chlorophillipt) and dexpanthenol, a repellant of synthetic (ethacridine lactate) origin [26]. Scientist Soleiman A. conducted the pharmacological study of the combined ointment “Phyiolet” [27]. The experiments determined the wound healing, antimicrobial and anti-inflammatory effects of “Phyiolet” ointment. By its spectrum of the pharmacological action found “Phyiolet” ointment can be recommended for the local treatment of wounds and superficial skin burns of the first and second stages of the wound process, non-allergic contact dermatitis [27].

Garkavtseva O. A. substantiated the composition and technology of “Dermalik” ointment for the treatment of atopic dermatitis [28]. The pharmacological and microbiological studies determined the anti-inflammatory, anti-allergic and antimicrobial effects of the drug [28].

Bezditko K. P. studied “Estan” ointment containing the extract of horse chestnut (Aesculus hippocastanum) seed, the oak bark extract, and lidocaine hydrochloride, which was created to treat hemorrhoids [29]. It has been shown that “Estan” ointment has the anti-inflammatory, analgesic, reparative, locally anesthetizing, antimicrobial, vessel-protective effect. The ointment has a high degree of safety, does not show allergic and local irritative effects. By the spectrum of the pharmacological action “Estan” ointment corresponds to the directions of pharmacotherapy for hemorrhoids [29].

Based on the analysis of the results of technological, physicochemical, biopharmaceutical, microbiological and biological studies Pavkh O.I. developed the optimal composition and substantiated the rational technology of a soft nasal form as an emulsifier with herbal infusions and essential oils [30]. According to the results of the pharmacological studies the antimicrobial, anti-inflammatory and reparative activity of “Rhinitistop” ointment was determined [30].

Havkaliuk M. I. developed the optimal composition and substantiated the rational technology of an anti-cellulite medicinal cosmetic agent on the emulsion base with plant extracts and essential oils [31]. The pharmacological studies determined the anti-edema and capillary-protective properties of the ointment, which would have an impact on the main pathways of cellulite pathogenesis [31].

Nazen B. M. found that the oil of grapes seeds had a marked anti-inflammatory and reparative effect [32]. It was shown that the oil of grapes seeds had a high degree of safety, did not exhibit the local irritative and allergic action [32].

Burd N. B. conducted the systematic phytochemical, pharmacological and anatomical study of some representatives of the Amaranthus genus of the flora of Ukraine [33]. The optimum conditions for obtaining a complex of lipophilic substances from the above-ground part of amaranthus were substantiated. It was found that the lipophilic fraction of amaranth and the cream on its basis had the anti-inflammatory and wound healing effects [33].

The thesis of Kuchynska I. V. is dedicated to the study of the pharmacological activity of new ointments based on chloroform and freon extracts of the lipophilic complex from aspen bark “Tremulin” [34]. For the first time the anti-inflammatory, antimicrobial, analgesic, reparative effects of the ointments under study were substantiated theoretically and proven experimentally [34].

The work of Khalavka M. V. is devoted to the development of a soft combined medicinal product based on the dry extract of licorice root, anaesthines and nitazolum of “Glitacid” ointment [35], and the study of Berezniakov A. V. is devoted to the pharmacological study of anti-inflammatory and reparative properties of this medicinal product [36]. “Glitacid” ointment is safe, exhibits pronounced reparative and anti-inflammatory properties confirmed by increased durability of postoperative scars of aseptic and infected linear wounds, accelerated processes of cleaning of full-wound skin wounds, increased speed of epithelization of the plane wound, the inhibitory action on the activity of nutrient amines, cyclooxygenase and lipoxygenase metabolism of arachidonic acid [36].
Serdiuk Ie. V. developed a scientific and methodical approach to the creation of the ointment with a complex action with the content of the plant raw material for the treatment of wounds in the first phase of the wound process [37]. The composition of "Phrayd" ointment with the content of a thick extract of ash tree bark and benzocaine was substantiated theoretically and experimentally. The preclinical studies of the ointment developed were performed, and the specific reparative activity and safety of the medicine were proven [37].

Based on physicochemical, technological, biopharmaceutical, pharmacological and microbiological studies of a thick extract of oak bark scientist Khokhlenkova N. V. conducted a pharmaceutical development of "Biotanin" and "Bioflorin" ointments on its basis, and "Algi-Cord" napkins for the complex treatment of the wound process. The stability and pharmacological activity of the drugs developed were proven [38].

The work of Tkachova O. V. is devoted to the pharmacological study of new combined medicines with active components of natural origin and substantiation of their application in different phases of the wound process (WP) [39]. It was determined that the spectrum of the pharmacological action substantiated the use of "Prolidoxid" ointment for the treatment of purulent wounds and superficial skin burns in the first phase of WP and in transition to the second phase, "Bioflorin" ointment for pharmacotherapy in the II-III phases of WP; "Zhyvitan" gel – in II-III phases of WP and venous trophic ulcers against the background of chronic venous insufficiency [39].

The thesis of Horlachova V. I. is devoted to the search and development of the technology of a new cream with the lipophilic extract from wild carrot seeds (LEWCS) for the treatment of mild burn wounds [40]. The preclinical pharmacological studies proved the wound healing activity and safety of LEWCS and the cream with LEWCS [40].

The thesis of Kran O. S. is devoted to the creation of a new combined drug for local wound healing in the second phase of the gel-shaped wound process for use in therapy and surgery [41]. The pharmacological and microbiological studies determined the anti-allergic, reparative and antimicrobial effects of the drug [41].

Scientist Esam Zurgani Ahmed Zeghdani conducted the pharmacological study of a new combined ointment "Allergolic" on the basis of a dry extract of licorice root intended for pharmacocorrection of allergic dermatitis, including those complicated by the secondary fungal infection, and determined the anti-inflammatory, antiallergic, immunotrophic and antimicrobial activity and some mechanisms of its therapeutic action [42]. The toxicological studies have proven that the combined "Allergolic" ointment is safe, does not show the locally irritating, allergic and toxic skin resorptive action [42].

Therefore, taking into account the above results of the analysis of the results of the research of the Ukrainian scientists the conclusion can be made that the search and pharmacological study of new potential medicinal products for the treatment of skin lesions containing biologically active substances from the plant raw material continue. However, the data presented indicate that the use of food plants as a source of BAS is very limited and does not correspond to their high potential.

CONCLUSIONS
1. In the process of theoretical substantiation by the analysis of domestic and world databases of scientific information the expediency and relevance of the search for potential medicinal products containing biologically active substances of natural origin among the raw material of food plants of the Apium genus, in particular carrot and parsnip have been proven.

2. It has been determined that plants of the Apium genus – carrot and parsnip roots having a powerful, affordable and cheap raw material base are the sources of substances containing the amount of biologically active substances that are promising for the creation of new medicinal products on their basis with the cytoprotective, anti-inflammatory, nephroprotective, wound healing, reparative action.

3. It has been proven that the search, creation and pharmacological study of new medicinal products based on the food plant raw material, in particular carrot and parsnip roots, in order to introduce into medical practice for the treatment of skin lesions, are relevant, expedient and timely.

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