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Production Technology of Phytopreparations Based on Essential Oils

Zh.R. Shaimerdenova

International research and production holding "Phytochemistry", 4 Gazaliev str., Karaganda, Kazakhstan

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Abstract

The article provides an overview of phytopreparations technology based on essential oils, in particular: criteria for the selection of components, qualitative and quantitative compositions analyzes, parameters of the technological cycle of production of drugs, problems of standardization and quality control of stages of the production of original drugs. A number of standard samples based on terpenoids for phased quality control of the production of medicinal products are described, which are included in the European, Kazakhstan and Japanese pharmacopeias. The main countries producing essential oils and their components, as well as manufacturers of phytopreparations based on them are indicated. The modern technologies for the production of essential oils from plant materials are reviewed, namely: microwave and ultrasonic extractions, supercritical carbon dioxide extraction and micro-steam distillation with solid phase microextraction. The dosage forms of preparations based on essential oils (tablets, ointments, gels, oil solutions, suppositories, sprays, aerosols, nanocapsules), their relationship with bioavailability and therapeutic effect are discussed. Promising dosage forms that ensure dosage accuracy for the targeted action of drugs based on essential oils have been identified.

1. Introduction

In modern conditions, the problem of developing and standardizing drugs based on plant materials is becoming more and more urgent, while essential oil plants occupy a special place. First of all, this is due to the high demand for essential oils for perfumery, cosmetic, pharmaceutical, food production, as the component composition of many essential oils of widely used essential oil plants is quite stable and well studied. Essential oils have an extensive spectrum of biological activity, have low toxicity in recommended doses, and are available for mass use. The demand in the world market of essential oils in 2018 was 226.9 kilotons [1].

Essential oils are found in plants, as a rule, in small amounts – 0.01–1.0%, although there are species containing up to 90% [2]. The technologies for the isolation of essential oils are very diverse, pharmacopoeial methods are usually used for their production: steam distillation, extraction, concentration on solid sorbents and cryo-traps, and entrainment. Modern methods for the isolation of essential oils, such as microwave, ultrasonic, supercritical carbon dioxide extraction, micro-steam distillation with solid-phase microextraction, also find application [3].

The State Register of Medicines and the Vidal Drugs Directory contain data on more than 80 types of drugs, which contain essential oils or their components. Preparations based on essential oils and terpenes are widely used as anti-inflammatory, wound healing, antiseptic, antibacterial agents, in the treatment of diseases of the upper respiratory tract and inflammatory soft tissues, biliary tract and gastrointestinal tract.

It is well known that the most important issue in the creation of phytopreparations is the standardization and increasing the level of objective assessment of their quality. However, it must be recognized that due to the heterogeneity and multicomponent composition of essential oils, the issues of standardization of phytopreparations based on them to this day, in most cases, remain open.

*Corresponding author. E-mail: arsenzhan@bk.ru

This problem can be solved only when using in the analysis of medicinal plant materials, substances and drugs containing essential oils, standard samples of a terpenoid nature, i.e. the main class of active substances that make up both the feedstock and the finished drug. Traditionally, essential oils are standardized in terms of physical (density, rotation angle of polarized light, refractive index, freezing point, melting, boiling) and chemical indicators (ether and acid number, ether number after acetylation). The development of new methods of analysis and the creation of an analytical base of organic compounds contributed to a more detailed and subtle analysis of essential oils. The development of chromatographic separation methods and spectral characteristics of organic substances, including mass spectrometry, made it possible to isolate and determine the structure of natural compounds of essential oils [4]. This makes it possible to more accurately standardize essential oils containing a wide variety of compounds with biological activity. At the same time, the issue of organizing the production of standard samples of terpenoids, which is still poorly developed, remains relevant, due to the complexity of the isolation technology and the instability of essential oils and their components.

2. Modern technologies for the production of essential oils

Recently, many published works on the chemical study of essential oils and their industrial production have been devoted. Isolation of essential oils is mainly carried out by scientific centers of the United States of America, China, Turkey, India, Russia, which use new methods and optimize the conditions for the complete extraction of essential oils.

The first place in the volume of world production of essential oils is occupied by the countries of South and North America and is 40%, the second place is taken by the countries of Asia – 30% and the third place by the countries of Europe – 25% [5]. It is known that Bulgaria produces essential oils of *Rosa*, *Lavandula*, *Mentha* and *Melissa*. In the cultivation of *Rosa* essential oil, Bulgaria ranks second after Turkey. The main producer of *Lavandula* essential oil is France in the southeastern region of Provence and accounts for 90% of world production. Other countries-producers of *Lavandula* essential oil are Spain, USA, Russia, Italy, New Zealand, Australia, India, Argentina, Brazil, South Africa and the Balkan countries [6].

The main producers of *Rosmarinus* essential oil are Spain and Tunisia, which cultivate 100–350 t per year [7]. World production of *Mentha* essential oil is about 20 000 t, of which 70% is from India. The main producers of essential oil are China, Brazil, Japan, France and the United States of America.

The USA cultivates citrus and mint oils, Brazil – eucalyptus, sassafras, citrus oils. On the island of Réunion, located in the east of Madagascar, *Geranium* oil is cultivated.

In the industrial production of essential oils, steam distillation is used, thus a number of companies have introduced interstate standards for essential oils from *Rosmarinus*, *Mentha* («Kazakhstan Business Solution», Kazakhstan) [8, 9] *Lavandula*, *Coriandrum* fruits, *Rosa*, *Corymbia citriodora* («Parfumest», Moscow, Russia) [10–13].

For the production of essential oils, various modifications of the hydrodistillation method have also become widespread, which, due to their technological disadvantages, actualize the issue of developing effective, resource-saving technologies. The use of innovative extraction methods reduces the duration of the process, ensures the safety of the used solvents, the quantitative yield of the target substance, avoiding the destruction of its molecule. The technology for extracting essential oil from *Haematococcus pluvialis* algae, *Piper* biomass and *Cannabis* was developed by Sustainable Aquatics Inc., a distinctive feature of this method is the combination of the stages of grinding raw materials in a ball mill and extraction with ethyl alcohol, which allows to reduce the production process, while grinding the raw materials on a ball mill increases the yield of components of essential oils [14].

The multi-level continuous steam distillation unit developed by Yingkou Chenguang Extracted Plant Equipment Co (Yingkou, China) allows reducing production costs and improving the quality of the produced oil [15].

In the work of [16] proposed a two-stage method for isolating the extraction of essential oils of coniferous wood: in the first stage, a CO_2 extract is obtained, and then distillation with hot steam from a CO_2 extract is used. This method allows to reduce the duration of the process by 2 times with the quantitative content of the target substances in comparison with the oil obtained by traditional technology.

The authors of [17] also proposed the use of CO_2 extraction to extract the components of the es-

sential oil from *Salvia officinalis*. In the course of experiments on CO_2 extraction of *Salvia officinalis* raw materials, the optimal regime was determined in which the yield of the components of the essential oil was 2 times higher compared to traditional technology.

The researches of [18] have patented a method for extracting biologically active compounds from plant materials by the simultaneous use of ultrasound and microwaves in a laminar regime of a continuous extraction stream under controlled conditions at temperatures that do not affect the structure of thermolabile biologically active compounds. Using this method essential oils, mixtures of polyphenols, anthocyanins, terpenes, stabilized proteins that cannot be obtained by other methods, are obtained.

3. Technology of soft dosage forms based on essential oils

In the production of phytopreparations based on essential oils, soft dosage forms have been widely used. One of these forms is ointments intended for application to the skin, wounds or mucous membranes. Drugs with essential oils such as «Geucamen», «Doctor Theiss, Eucalyptus», «Gold Star Balm», «Linkus Balm», «Doctor Mom», etc. are known. The composition of these ointments includes essential oil of *Mentha*, *Eucalyptus* oil, anethol (1), menthol (2), camphor (3), thymol (4) and eucalyptole (5) [19, 20].

There are a number of ointments with anti-inflammatory, antiviral, wound-healing effects, as well as for the treatment of thermal burns, some of which are already used in medical practice [21–22].

Ointments are prepared by mixing the essential oils with an ointment base. When developing ointments, it is necessary to consider a stable basis, since there are developed ointments based on animal fat (pig fat), which reduces the shelf life, and therefore the range of bases for ointments and their choice depending on the application are increased, while maintaining a therapeutic effect, thereby allowing to improve the technology of ointments.

The National University of Pharmacy (Kharkiv, Ukraine) has developed and standardized «Dermalik» ointment for the treatment of atopic dermatitis, containing dense extract of *Glycyrrhiza* roots, essential oils of *Marticaria* and *Melaleuca*. The identification of essential oils was carried out by gas liquid chromatography, the active ingredient in *Marticaria* essential oil is chamazulene, for *Melaleuca* oil - terpene-4-ol. The ointment base was prepared by phase inversion, wax and emulsifier No. 1 were melted at a temperature of 70±5.0 °C and a dense extract of *Glycyrrhiza* roots dissolved in the hydrophilic phase of the ointment base was added with stirring. Essential oils were dissolved in *Zea* oil at room temperature and introduced into the oil phase of the emulsion system. As a result of the development of the ointment, indicators of the quality of the studied drug were established and its stability was studied [23].

Suppositories are the second most common among soft dosage forms, and, depending on the biologically active substance, they can be used in the form of a multicomponent dosage form, for example, the «Rectofit 1» suppository [24], including essential oil of *Eucalyptus viminalis*. Suppository «Rektofit 1», which include three components of candle: the first (phytopropolis suppository) propolis extract and essential oils of *Abies*, *Juniperus*, *Melaleuca*, *Eucalyptus*. The second – liquid components – extract of *Makleaya*, *Kavir*, *Polygonatum*, etc. The third – powder extracts – bitulin, chitosan, etc. Candles are produced as follows: comminuted propolis is poured with 96% alcohol for 3–5 days, then propolis is mixed with Paker-21 *Palmae* oil and Rican DMG type P (B) emulsifier melted in a water bath, then alcohol is distilled off, next the mixture is diluted with Paker-21 *Palmae* oil, the mixture is brought to a temperature of 35–36 °C and essential oils of plants, *Makleaya* herb extract and microcarpous ethanolic, *Hippophae* oil and betulinol (powder) are injected, after which the whole volume is mixed with the injected components and filled in forms using a dispenser. Thus, the resulting composition can be used in the form of rectal or vaginal suppositories.

(1) (2) (3) (4) (5)

Suppositories «Rektofit 2», possessing an antitumor effect, is produced on the similar ointment base as «Rectofit 1». Essential oils of *Abies, Juniperus communis*, *Melaleuca*, *Eucalyptus viminalis* and alcoholic extracts of microcarpous *Makleaya* herb, sprouts of ethanolic potato and *Nigella sativa* oil, betulinol (powder) were used as active substances. The drug is made in the form of rectal or vaginal suppositories [25].

4. Technology of solid dosage forms based on essential oils

In the pharmaceutical market, solid dosage forms based on essential oils are represented mainly by lozenges, pastilles. Many authors emphasize lozenges as one of the most effective for the treatment and prevention of diseases of the oral cavity and throat [26, 27]. Important in the technology of medicinal products are excipients used to obtain the dosage form. In the development of lozenges, great attention is paid to the group of corrective excipients, accounting for up to 55%. Of the total number of lozenges, only 17% contain substances of natural origin [28]. A wide range of tablets with essential oil is presented on the market of drugs, namely "Agisept® with menthol and eucalypt", "Doctor Theiss, Angisept", "Pektusinum", "Septolete", etc.

Pectusinum is a medicinal product for the treatment of inflammatory diseases of the upper respiratory tract, containing levomenthol, oil of *Eucalyptus* leaves, *Mentha piperita* as active substances. Pectusinum is produced as follows: sugar granules are obtained, for this, sucrose, colloidal silicon dioxide, sodium carmellose are mixed and moistened with water, wet mass is granulated through a sieve, sugar granules are dried to a residual moisture of 0.8–1.3% and dry granulation is carried out. Then, moistened beta-cyclodextrine and/or aluminum magnesium silicate with dissolved menthol in ethanol are mixed in a container and the wet mass is granulated through a sieve, followed by drying and grinding the dry mass in a mill. Sugar granules and a complex of beta-cyclodextrin and /or aluminum magnesium silicate with menthol and an alcohol solution of Eucalyptus oil and *Mentha piperita* are mixed in the mixer. Next, the talcing of the mass with talc and stearic acid or its salts is carried out. Pectusinum is available in pill form [29].

To expand the range of oral medications, it is rational to use nanocapsules, since this dosage form is able to store and deliver lipophilic substances in a form that is easily accessible to the body – a solution.

Encapsulation of drugs and biologically active food additives has been widely used in medical practice as one of the effective means of their controlled delivery in the human body [30].

It is known that essential oils are unstable and subject to oxidative transformations in the presence of oxygen, light and temperature. Therefore, attempts have been made to maintain the composition of essential oils and their biological activity by encapsulation in various colloidal systems, such as microcapsules, microspheres, nano- and microemulsions and liposomes.

The article [31] describes the influence of the nature of essential oils and other factors (composition of lipid vesicle membranes, cholesterol content, molar ratio of essential oils to lipids, preparation method) on liposome characteristics, such as size, encapsulation efficiency and thermal behavior of lipid bilayers. It was found that some essential oils can reduce the size of liposomes, homogenize liposomal dispersions, increase fluidity and reduce the oxidation of the lipid bilayer. In this case, liposomes can protect the fluidity of essential oils and remain stable at 4–5 °C for 6 months. Thus, liposomes encapsulating essential oils are promising dosage forms that can be used to increase the antimicrobial activity of essential oils, to study their effect on cell membranes, and to provide alternative therapeutic agents for the treatment of diseases.

The Institute for Agricultural Processing (China) has developed a nanocapsule with essential oil [32], the technology for which is as follows: camphor is added to the reaction vessel with deionized water and mercapto-modified chitosan (in a ratio of 2.0–0.5), an emulsifier (glycerol monostearate) and a co-emulsifier are mixed for 30–60 min, changing the mixing mode for 15–30 min at 10000–15000 rpm, the result is an emulsion. Then the mixing speed is reduced to 300–600 rpm and a solution of a crosslinking agent is added and stirring is continued in a water bath at 50 °C for 1–3 h. After completion of the reaction, the solution is filtered, washed with distilled water, and after freeze-drying, nanocapsules with essential oil are obtained.

The use of modern technologies, namely, nanocapsulation based on essential oils, allows you to mask the color, taste, smell of the substance, reduce the toxicity of the active substance, the gradual release and prolongation of the active substance, increase the shelf life of the drug, enhance the properties of the substance and to obtain drugs in the form of various nanostructures.

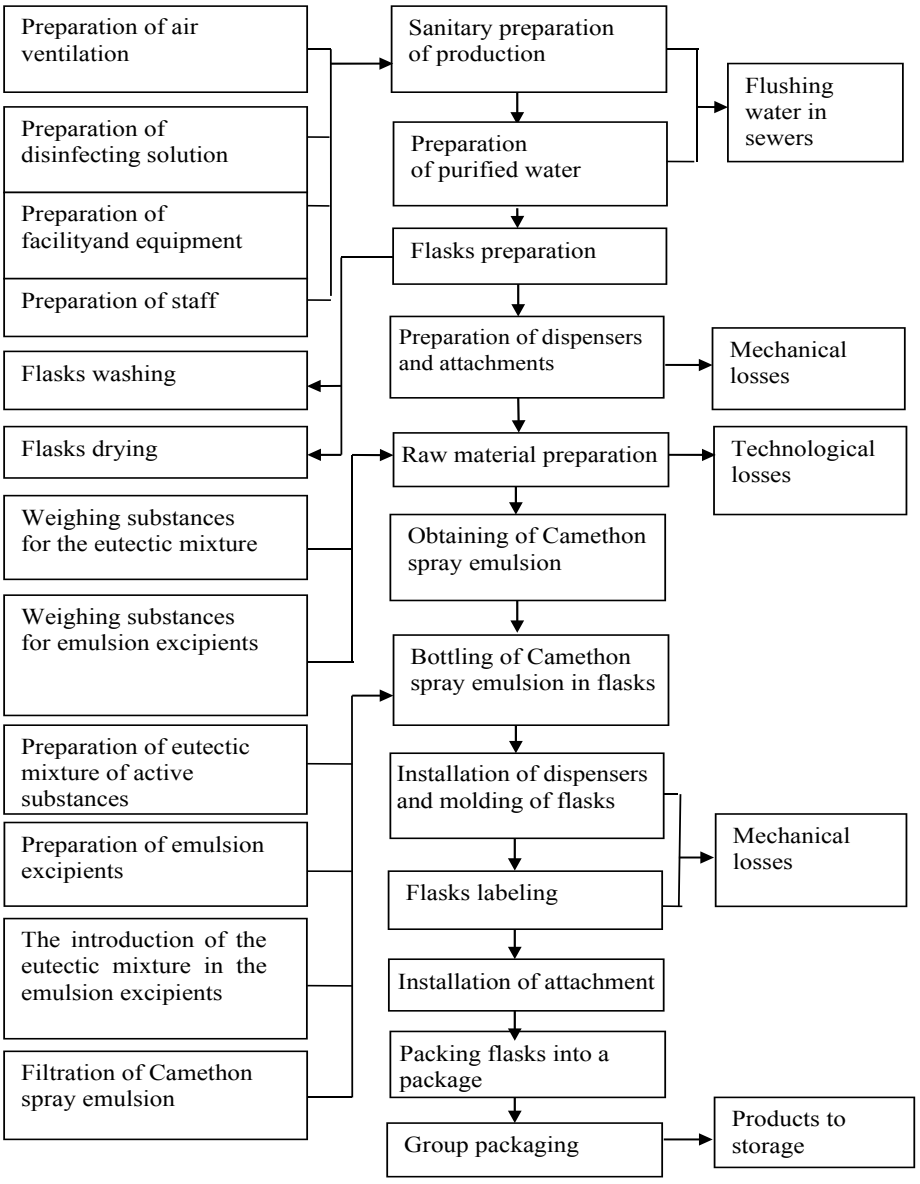
5. Technology of liquid dosage forms based on essential oils

Liquid dosage forms represent as free dispersed systems in which drug substances are distributed in a liquid dispersion medium. Such drugs with essential oils as "Tincture of eucalyptus", drops "Urolesan", "Urocholesan", "Pinosol", "Carmolis", etc. are known.

Spray is the original dosage form that provides effective delivery of the drug composition to the human body. Examples of common sprays are Ingalipt, Kameton, Xylometazoline Eucalyptus, etc.

A company "VIPS-MED" (Moscow, Russia) developed a new dosage form capable of spraying without excessive pressure and the use of propellant [33]. A process flow diagram for the manufacture of the drug "Camethon-Spray" is proposed (Scheme). Spray production method is as follows: in round-bottomed flask paraffinic oil and emulsifiers (emulsifier "Hard-2" (H-2), Tween-80 (Polysorbate 80) are loaded and with constant stirring, the mixture is heated in a water bath. Separately, distilled water is heated to a temperature of 75 °C, added to the flask and emulsified for 10–15 min, then cooled to 18–20 °C and the active substances are loaded (chlorobutanol hydrate, camphor, menthol, eucalyptus oil) and stirring is continued for 10–15 min [34].

Thus, a new drug composition is stable, due to a sufficient amount of vaseline and the active ingredients (chlorobutanol hydrate, camphor, menthol, eucalyptus oil) have a prolonged effect, thereby achieving a good therapeutic effect.



Sheme. Technological process scheme for the production of the drug "Camethon-Spray".

On the basis of *Mentha piperita* oil, the combined drug "Inhalipt" is produced, which is used in infectious diseases of the upper respiratory tract [35]. For production of biologically active substance, thymol is dissolved in a mixture of *Eucalyptus* and *Mentha* oils. Then, Polysorbate 80 (Tween) and benzalkonium chloride in eucalyptus extract are mixed. Then the obtained solutions are mixed and an active biological substance of green color is received. To obtain the drug of local action "Inhalipt active plus" purified water is mixed with glycerin, followed by the addition of an active biological substance. The developed drug "Inhalipt active plus" can be used not only for internal use, but also for external use as an antiseptic for scratches and burns.

The next phytopreparation based on essential oils is Abisil – an oily 20% solution for local and external use, manufactured by the pharmaceutical company "Tatkhimpharmpreparat" (Kazan, Russia). A biologically active base is obtained from *Abies* by steam distillation for 7–10 h and its standardization is carried out. The terpenoid composition is a thick liquid from yellow-transparent to milky white with a specific smell and has certain chemical and physical constants. According to gas-liquid chromatography, the amount of monoterpenoids is 33% by weight of the taken mixture, and the content of monoterpenoid bornyl acetate is no less than 10.0% of the total composition of terpenoids. The preparation "Abisil – oily 20% solution for local and external use" is made from the obtained substance by dissolving this substance in oil – olive, sunflower or soya [36]. *Abies* terpenoid substance is polyactive, possessing increased wound healing, anti-inflammatory, antibacterial, immunomodulating, analgesic and antitumor activity. The developed terpenoid substance can be used in various drugs, in which it exhibits high therapeutic efficacy and has a long shelf life.

6. The standardization of phytopreparations based on essential oils

Currently, the problem of standardization of drugs of international and domestic manufacturers is not fully resolved due to the lack of standard samples of drugs registered in the Pharmacopoeia, which leads to an increase in the share of falsified phytopreparations in the pharmacy network. Therefore, it is necessary to develop standardization techniques that guarantee the quality, purity and safety of the drug for the consumer.

According to pharmacopoeias of countries of world manufacturers of phytopreparations, standardization begins from the collection of raw materials to the receipt of the finished dosage form. The quality control of essential oil raw materials is carried out according to pharmacopoeial articles: the identity or authenticity of the raw materials, the absence of impurities, numerical indicators, microbiological purity, quantitative content of the active substance [37]. The main technological criteria are the volume of industrial stocks and the content of essential oils.

In addition to studying the organoleptic and physic-chemical properties of essential oils, components are identified by chromatographic methods. Among modern methods for identifying components of essential oils, gas-liquid chromatography, gas chromatography-mass spectrometry with a mass-selective detector, gas chromatography with a flame-ionization detector using electronic libraries Wiley, MassFindersoftware 4.0, Adams, Baser should be noted. This makes it possible to more accurately standardize essential oils containing a wide variety of compounds with biological activity.

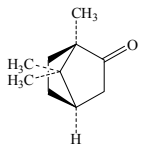
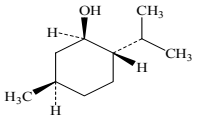
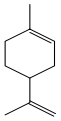
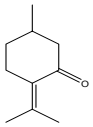
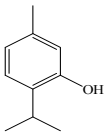
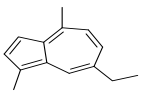
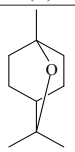
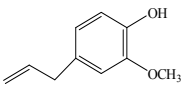
Identification of the main components in the essential oil is carried out by chromato-mass spectrometry, comparing with the retention indices of the components with reference samples. Terpenoids are used as reference materials: (-)-α-pinene, (+)-α-pinene, (-)-camphene, (+)-camphene, (+)-β-pinene, (-)-β-pinene, sabinene, (+)-limonene, (-)-limonene, (-)-linalool, (±)-linalool, (-)-α-terpineol, eugenol [38], thymol, menthol, 1,8-cineol [39].

Standard samples of medicinal substances allow to control the quality of the phased production of drugs, as well as the need to provide test laboratories engaged in quality control of drugs and medicinal raw materials with state and working standard samples.

According to the data of the State Pharmacopoeia Center of the Ministry of Health of the Republic of Kazakhstan, International Research and Production holding "Phytochemistry" introduced for the first time fourteen domestic standard samples: arglabin, artemisinin, achillin, harmine, grossheimin, leukomisine, limonene, pinostrobin, pulegone, stachydrine, chamazulene, cynaropicrin, ecdysterone, echinopsine [40].

In terms of comparative analysis, the standard samples used in the manufacture of medicinal preparations based on essential oils that are available in the European, Kazakhstani and Japanese Pharmacopoeias are listed in Table.

Table
Standard samples, most commonly used to control the quality of drug production

#	Standard sample	Structural formula	Name of pharmacopeia	Drugs	Source of isolation
1	Camphor	 (1)	Temporary Pharmacopeia article of the Republic of Kazakhstan 42-1622-04 Included in the European Pharmacopoeia 01/2008:1400 [41]	Spray Aspekton Krewel Meuselbach GmbH (Germany) Ointment Agicold-PlusAgio Pharmaceuticals, Ltd. (India) Ointment Alvipsal ZAO «Altayvitamin» (Russia) Solution Camphor alcohol 10%, 30 ml solution Shansharov-Farm, Santo Member of Polpharma Group (Kazakhstan) Solution Carmolis Iromedica (Switzerland)	*Artemisia* leucodes Schrenk [42]
2	Levomenthol	 (2)	Included in the European Pharmacopoeia 01/2008:0619 [41] Included in the Pharmacopoeia of Japan [43]	Ointment Lincus Balm Herbion Pakistan, Private Limited (Pakistan) Ointment Moov Paras Pharmaceuticals, Ltd. (India) Sparay Pinosol® Zentiva, a.s. (Slovakia) Pastilles Eucalyptus – MOOO «Valeant» (Russia)	*Mentha* piperita L. [44]
3	Limonene	 (3)	Included in the Pharmacopoeia of the Republic of Kazakhstan [40]		*Citrus aurantiifolia* (Christm.) Swing [45]
4	Pulegone	 (4)	Included in the Pharmacopoeia of the Republic of Kazakhstan [40]	Ointment Dcotor mom® phyto Unique pharmaceutical Laboratories (India) Ointment Efcamon JSC «NizhFarm» (Russia)	*Ziziphora clinopodioides* Lam. [46]
5	Thymol	 (5)	Included in the Pharmacopoeia of Japan [43] Included in the Pharmacopoeia of the Republic of Kazakhstan [47] Included in the European Pharmacopoeia 01/2008:0791 [41]	Ointment Dcotor mom® phyto Unique pharmaceutical Laboratories (India) Ointment Efcamon JSC «NizhFarm» (Russia)	*Thymus vulgaris* L. [48]
6	Chamazulene	 (6)	Included in the Pharmacopoeia of the Republic of Kazakhstan [40]	Solution Romazulan Biofarm (Romania)	*Artemisia arborescens* L. [49]
7	1,8- cineol	 (7)	Temporary Pharmacopeia article of the Republic of Kazakhstan 42-1325-04 Included in the European Pharmacopoeia 01/2008:1973. [40]	Capsules Soledum Klosterfrau berlin Gmbh (Germany)	*Achillea tomentosa* L. [50]
8	Eugenol	 (8)	Refractive index: From 1.540 to 1.542 Included in the European Pharmacopoeia 01/2008:1100. [40]	Eugenol-antiseptic and analgesic fluid JSC «SEZ «Vladmiva» (Russia) Bittner's Drops Bittner (Austria)	*Eugenia caryophyllata, Ocimmum gratissimum* [51]

As it can be seen from Table 1, the number of standard samples of components of essential oils necessary for the phased control of the quality of original preparations based on multicomponent essential oils and included in pharmacopoeias is not enough for a complete analysis of the chemical composition, which is primarily due to their high lability and complexity of the production technology.

As a successful experience in the use of essential oils and its components in the manufacture of phytopreparations, we can cite the example of the manufacturing pharmaceutical company "Vifiteh" (Moscow, Russia), which produces drugs based on plant materials. The company has registered 100 types of drugs. The specialized laboratory of "Vifiteh" carries out phased quality control of drugs and improves methods for the standardization of phytopreparations [52]. In the analysis of the authenticity of phytopreparations, standard samples of terpenoids are used: bornyl acetate for the preparation "Urohol", menthol, cineol – "Pectusin", tyrosol – "*Rhodiola* liquid extract", eucalymin – "Chlorophyllipt". To standardize the preparations "*Hippophae* oil" and "*Rosa* oil", standard samples of linoleic, linolenic, myristic, palmitic, stearic acids are used. However, for phased control of the quality of drugs, "Vifiteh" uses standard samples of foreign production: the Sigma-aldrich company, the experimental plant of the State National Center of Drugs (Kharkiv, Ukraine), and the Institute of Plant Chemistry named after Academician S.Yu. Yunusov (Tashkent, Uzbekistan), such as atropine, arbutin, bornyl acetate, vincamine hydrochloride, galantamine hydrobromide, glaucine hydrochloride, galacturonic acid, cineol, emodin (frangula-emodin), ecdistine, erisimine, etc., which are associated with the complexity of the technology of separation and the instability of essential oils and its components.

The standardization of phytopreparations for liquid dosage forms due to the complex composition of the substances (aloe juice, aloe extract liquid, *Viburnum* syrup, *Kalanchoe* juice, cardiotron, lespefril, tincture of *Schisandra*, *Radiola* liquid extract, urochol, *Thermopsis* syrup with *Glycyrrhiza*, *Rosa* oil, *Eleutherococcus* liquid extract) is carried out by quantitative content of active and related substances.

Thus, the use of standard samples for phased quality control, production of drugs, also registered and implemented in the pharmacy network of drugs, allows you to timely determine the falsification and to provide quality control of pharmaceutical production according to Good Manufacturing Practice standards.

7. Conclusions

Thus, the conducted analysis of literature data over the past 10 years indicates that standardized phytopreparations are used in the pharmaceutical market based on essential oils, which are used both for local and internal use.

At the same time, a significant drawback of the technology of phytopreparations based on essential oils is the high cost of the substance due to the low yield of the active substance, the complexity of the obtaining technology and the lability of the components of the essential oil, which also causes complexity of organization of phased control of the quality of phytopreparations production due to the insufficient number of standard samples of terpenoids registered in pharmacopoeias. According to the above-said, it is necessary to introduce innovative methods of raw materials extraction, such as ultrasonic, solvent-free microwave extraction, supercritical carbon dioxide extraction, microwave extraction with solvent and micro-steam distillation with solid-phase microextraction. At the same time, modern technologies of finished dosage forms of preparations based on essential oils, allows along with traditional ointments, gels, oil solutions, suppositories, dosage forms with directed action and controlled release like sprays, aerosols, nanocapsules are produced.

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