










The Current State and Prospects for the Use of Herbal Medicines for Wound-Healing and Anti-Inflammatory Action in Kazakhstan: A Literature Review

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Abstract

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BACKGROUND: As dosage forms, oils, drops, ointments, solutions, films, and suppositories represent phytopreparations for external use. The use of the drug “Kyzyl mai” in clinical practice pursues the achievement of wound-healing (including anti-burn effect), anti-inflammatory, reparative, metabolic, antibacterial, antiviral, and analgesic effects.

AIM: We aimed to analyze the range of soft dosage forms in the form of suppositories with herbal components in their composition, used as anti-inflammatory and wound-healing agents.

METHODS: The design in this study was a literature review article. Search for articles using relevant ones obtained from data based on PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar obtained 283 articles.

RESULTS: There are 12 articles that are relevant and discuss their content and use in the health.

CONCLUSION: This review presents new dosage forms have been created – medicinal film “Fiadent,” medicinal film “Normophyt,” medicinal film with Piyavit. On the basis of chamomile extract obtained by supercritical carbon dioxide extraction, the optimal composition and technological scheme for the production of anti-inflammatory suppositories for use in proctology have been developed. The article describes a literature review of suppositories of anti-inflammatory action based on essential oil of balsamic poplar buds which have been developed.

Introduction

On the Republic of Kazakhstan territory, more than 6 thousand species of plants grow, belonging to different families and being sources of about 10 thousand compounds of various chemical classes used as cardiac drugs, antitumor agents, hormones, diuretics, antibiotics, and analgesics [1].

Studies conducted in Kazakhstan have shown that pharmacologically promising and industrially significant raw material for the isolation of chamazulene, 2,12'-bishamazulenil, and 1, 8-ceniol from essential oil can be a plant – *Ajania fruticulosa* (Ledeb.) from the Compositae family (Asteraceae) [2], [3], [4], [5], [6].

The component composition of the essential oil of *A. fruticulosa*, isolated by hydrodistillation on a Clevenger apparatus, was studied by chromatomass spectrometry. According to the analysis, 38 components were identified, among which the main

ones are: Chamazulene – 32.8%, 1.8-cineol – 18.8%, and β -myrcene – 7.3%. The high content of azulenes in the essential oil characterizes its anti-inflammatory and wound-healing properties, it is possible to use it to create new herbal remedies [7], [8], [9].

The rational combination of herbal preparations with various excipients, as well as the use of the optimal technological scheme for the manufacture of soft dosage forms for external use, significantly expands the therapeutic possibilities of herbal preparations for the treatment and prevention of dermatological and gynecological diseases.

As dosage forms, phytopreparations for external use are represented by oils, drops, ointments, solutions, films, and suppositories. The most widely represented dosage form are ointments (58%), followed by suppositories (15%), oils account for about 10%, solutions, drops, and films are approximately equal in proportion – 6% and 4%, respectively. The miscellaneous group includes such

dosage forms as sticks and plasters, accounting for about 3% [10].

According to the literature data, of interest is the arsenal of phytopreparations for external use as wound - healing and anti-inflammatory agents, such as ointments, oils, tinctures, solutions and various phytocompositions currently used for medical practice.

Wound-Healing and Anti-Inflammatory Phytopreparations for External Use

The main active ingredients of the domestic phytopreparation of polyphyletic oil "Kyzyl mai" are phytoncides, esters, resins, balms, fatty oils, vitamins, pro-vitamins, microelements, organic acids, enzymes, as well as small amounts of glycosides. The creators of the drug focus on the fact that "Kyzyl mai" contains bioactive compounds in physiological quantities, due to which it has a trigger mechanism of pharmacological action and this "Kyzyl mai" phytobalm compares favorably with wild rose and sea buckthorn ointments widely used in clinical practice. The use of the drug "Kyzyl mai" in clinical practice pursues the achievement of wound-healing (including anti-burn effect), anti-inflammatory, reparative, metabolic, antibacterial, antiviral, and analgesic effects [11].

An ointment of anti-inflammatory and wound-healing action based on oil with an oily extract of mountain ash has been patented [12].

The results of the histological study allow us to state that the ointment containing nitrofuril and sea buckthorn oil, on the model of burn wounds in rats, showed wound-healing activity comparable to the use of the reference drug – 20% «Solcoseryl» ointment. This means that it is possible to recommend using a combined drug as a wound-healing drug to treat purulent wounds, inflammatory infiltrates, mild and moderate burns, and pressure sores [13].

The composition and manufacturing technology of liniment with an extract of chamomile, *Calendula officinalis*, and yarrow have been developed. On models of wounds and thermal burns of the skin, the stimulating effect of liniment on reparative tissue regeneration was established. In terms of wound-healing and anti-burn action, liniment is not inferior to aloe liniment. Clinical studies conducted in gynecological and proctological clinics showed good tolerability of liniment and no side effects [14].

The study of the biological safety of emulsion ointments and gel with oil of narrow-leaved oleaster (*Elaeagnus angustifolia*) showed the absence of local irritating, general toxic, and sensitizing effects on the body of laboratory animals. About 10% and 20% emulsion ointments have a high therapeutic activity,

which allows them to be recommended for local therapy and allergic skin diseases. Gel with narrow-leaved oleaster (*E. angustifolia*) is recommended as a wound-healing agent and for treating of burns [15].

In the course of the study of the wound-healing effect of violet preparations on a model of a planar skin-muscle wound, a pronounced effect was revealed, in comparison with the control and the reference drug (infusion of calendula flowers), as evidenced by wound healing in a shorter time, as well as a more complete structural organization of the newly formed tissue, established during the cytological and histological study of granulations [16], [17].

Preparations from the leaves and shoots of eucalyptus have long been successfully used in medicine. The most widely used *Eucalyptus viminalis* Label (Myrtaceae), the leaves and shoots of which contain essential oil, phenolic aldehydes, chlorophylls, and tannins. The leaves and shoots of the eucalyptus are used as raw materials to produce drugs that have antimicrobial and anti-inflammatory effects. Eucalyptus oil and eucalyptus tincture are produced from it by standard methods. The antibacterial drug «Evcamin» was also received. For medical practice, chlorophyllipt is undoubtedly interesting, produced in 1% alcohol and 2% oil solutions, which have bactericidal and bacteriostatic activity against antibiotic-resistant staphylococci, *Candida*, *Klebsiella*, and other microorganisms, used as antimicrobial agents for external and internal use [18].

Externally, infusion and decoction of ivy leaves are used as a wound-healing agent, for burns, fungal infections of the scalp, and furunculosis [19].

As a result of the studies, the optimal compositions of two phytogels were developed and their wound-healing activity was tested on the model of a linear skin wound in animals with alloxan diabetes mellitus. According to its composition, Phytogel 1 includes an alcohol-water extract from St. John's wort, propolis and sea buckthorn oil, and excipients; Phytogel 2 – alcohol-water extracts from the noble laurel, *Echinacea purpurea*, licorice, sweet clover, aloe juice, individual preparation taurine, and a complex of excipients. The wound-healing activity of the developed gels in animals with experimental pathology of alloxan diabetes allows us to consider phytogels in the future to prevent and treat certain consequences of diabetes mellitus [20], [21], [22], [23].

Brown sphagnum extract in ethanol 20% has low toxicity and exhibits pronounced anti-inflammatory, analgesic, wound-healing, antibacterial, and antifungal properties in the experiment at the level of the reference drugs used [24], [25], [26].

Medicines prepared based on antlers, in the view of ancient Chinese doctors, increase the energy of the body, promote rejuvenation, treat blood and kidney diseases, improve wound healing, and normalize sexual function in men and women. Both in pure

form and combination with other therapeutic agents, they are widely used for anemia, exhaustion, general weakening of the body after infectious diseases, insufficiency of the cardiovascular system, slow wound healing, and others [27].

One of the favorite folk remedies is aloe (*Aloe arborescens*) – a plant of scientific medicine that can enhance the body's resistance. When administered parenterally, its preparations have a tonic, biostimulating effect. When taken orally in the form of a liquid extract, juice, and tablets, a juice effect is manifested, and there is a therapeutic effect in gastritis. When used externally, anti-inflammatory and wound-healing effects occur [28].

New dosage forms have been created - medicinal film "Fiadent," medicinal film "Normofit," medicinal film with Piyavit. Optimization of conducting biopharmaceutical studies on the study of bioavailability and kinetics of drug release from dosage forms by conductometry is proposed. The mechanism of release biologically active substances has been studied, making it possible to characterize the films as matrix systems of the diffusion type. Based on pharmacological studies, the presence of anti-inflammatory, regenerating, and immunomodulatory activity of plant extracts and their dosage forms was established [29], [30], [31], [32], [33], [34], [35], [36], [37].

Phytofilms are applied dosage forms containing purified complex extracts from medicinal plant materials with a wide range of indications [38].

Dental phytoplasty "Tonzinal," "Plates-CM-1," "Plates-CM-2," "Pharingal," "Alkogal," "Meglizal," and "Kardial" have a multilateral pharmacological action: Anti-inflammatory, antimicrobial, disinfectant, and tanning; improve regenerative and metabolic processes in the affected tissues, stimulate local immunity, strengthen blood vessels, and restore normal flora in the oral cavity. The composition of the original dental phytopreparations includes dry water-soluble lyophilized extracts of medicinal plants (St. John's wort, yarrow salvia, etc.), Vitamins C, B1, a complex of natural minerals, and gelatin [39].

The St. Petersburg Chemical and Pharmaceutical University conducts research on polysaccharides' chemical composition and pharmacological activity of such a widespread plant in the Russian Federation as the heart-shaped linden. The presence of antihypoxic, psychotropic, analgesic, anti-inflammatory, wound-healing, and immunotropic action was established to extract linden cordate, containing polysaccharides [40], [41], [42], [43], [44].

As a result of the complex and waste-free processing of milk thistle raw materials, the drug "Kamadol" was developed and recommended by the Pharmacological Committee of the Ministry of Health of the Russian Federation for use as an anti-inflammatory and wound-healing agent for external use [45].

To ensure a comprehensive impact on the main links of the pathogenetic process and minimize

the risk of side effects, especially in the treatment of chronic diseases in gynecology, it is necessary to use the resources of herbal medicine. LLC Research and Production Pharmaceutical Company "Eim" has developed an unparalleled complex preparation from herbal medicinal raw materials «Gynekofit», in the form of a complex tincture with 70% ethyl alcohol for the treatment of inflammatory gynecological diseases [46].

On the basis of bentonite clays of Tajikistan, an ointment

"Subinak" was developed, containing the essential oil of the small-flowered oregano and having antimicrobial activity [47].

As a result of an in-depth study of the essential oils of *Siberian* species of wormwood and yarrow, the azulene-containing drug "Akhizal" was proposed for clinical trials, intended to treat wounds, burn surfaces, and pyoinflammatory skin diseases [48].

The possibility of obtaining essential oil from the yarrow herb and an extract from the meal on the principle of low-waste technology was substantiated [49].

On the basis of the essential oil, the preparation "Akhizan" with wound-healing and anti-inflammatory action was obtained [50], a water-alcohol extract from yarrow meal after extracting the essential oil, containing a phenol-polysaccharide complex, is the main component of the antiulcer and gastroprotective agent "Akhigran" [51].

A fundamentally new direction in the treatment of wounds and burns is domestic topical medicines based on the essential oils of wormwood *Artemisia glabella* Kar. et Kir. [52].

As the analysis of the range of external dosage forms of herbal remedies shows, new developments in the field of drug technology using plant essential oils are promising for the treatment of various wounds.

However, the creation of dosage forms for external use does not allow achieving a systemic effect, but only locally. Hence, it is necessary to analyze the range of soft dosage forms in the form of suppositories with herbal components in their composition, used as anti-inflammatory and wound-healing agents.

Suppository Dosage Forms with Herbal Components of Anti-Inflammatory and Wound-Healing Action

The first mention of suppositories dates back to 2600 BC. The Ebers Papyrus describes laxative suppositories and those used for hemorrhoids [53].

Suppositories are described in Russian herbals, medical books, and handwritten pharmacopeias of the

XYI–XYIII centuries. They were made from soap or lard in the form of an “anchor carnation.” Sometimes mixtures of balsam, wood (olive) oil or honey and plant sap were heated and the molten mass was poured into paper molds [54].

In Russian folk medicine, cow butter was used as the basis for home-made suppositories, with which freshly crushed medicinal plant materials, honey, juices, and other active substances were mixed at room temperature, after which the mass was taken out into the cold. As needed, the required amount was separated from the “suppository” mass in a cone or cylinder with a pointed end and used in the form of a rectal dosage form [55].

The developed suppositories “Kyzyl mai with propolis” are distinguished by a mild and long-lasting anti-inflammatory, antibacterial, analgesic, and resolving the effect. Clinical observations confirmed the simulated pharmacodynamic orientation of suppositories «Kyzyl mai with propolis» [56].

On the basis of chamomile extract, obtained by supercritical carbon dioxide extraction, the optimal composition and technological scheme for the production of anti-inflammatory suppositories for use in proctology have been developed [57].

Anti-inflammatory suppositories based on essential oil of balsam poplar buds have been developed [58].

Moskalenko S.V. studied the acute toxicity of the developed suppositories, it was found that suppositories with mountain ash oil extract are practically non-toxic substances (class 6), $LD_{50}=5000$ mg/kg. Anti-burn, wound-healing, and anti-inflammatory effects have been established [59], [60].

Employees of the Scientific Center for Biopharmacy at the Research Institute of Perinatal Medicine and Obstetrics and Gynecology have been conducting research in recent years to create a new trichomikocidal preparations agent of plant and animal origin. As a result, trichomikocid vaginal and rectal suppositories have been proposed, with both systemic and local effects. The composition of the developed suppositories includes a phenolic complex [61].

Suppositories combined in composition for children with glycyram and anthrasennin are known, in which aloe dry extract is used as an anti-inflammatory component [62].

A new drug in the form of suppositories has been developed, the active ingredient of which is the plant substance “Limonidin,” which has a pronounced antioxidant, hepatoprotective, astringent, anti-inflammatory, antiviral, and antimicrobial effect [63], [64].

Created suppositories “Metrofit” – (metronidazole, polyphyletic oil) are a means of extended therapeutic action, antibacterial, anti-inflammatory, and reparative. The peculiarities of the

formulation allow summing up the positive effects of the ingredients [65].

Suppositories with sea buckthorn oil have been developed and introduced into medical practice as an anti-inflammatory agent. Suppositories combined in composition: The drug “Lipochromin - 800” rectocapsules with sea buckthorn oil and propolis vaginal suppositories with sea buckthorn oil [66], [67], [68].

As a wound-healing and anti-inflammatory agent, a composition was developed and suppositories with milk thistle oil were studied in an experiment [69].

With vesiculitis and prostatitis, suppositories with powder from comfrey roots and black poplar buds are effective, the action of which is mutually reinforcing. Poplar buds act as a strong antiseptic, and comfrey dramatically reduces inflammation. The alkaloids cynoglossin and lasiocarpine have analgesic properties, digallic acid has antimicrobial properties, and the alkaloid glyoxyldiuride enhances tissue regeneration [70].

The quality indicators of vaginal suppositories “Levoprox” containing chloramphenicol and propolis were studied. Full compliance of all quality indicators with the requirements of the relevant normative documents is shown. Vaginal suppositories “Levoprox” have a significant anti-inflammatory effect on models of experimental colpitis [71].

The composition and technological regulations for preparing suppositories containing the alcohol extract “BioR” have been developed. As a source of bioactive substances for preparing dosage forms, we used the “BioR” extract containing extractive substances from the strain of blue-green algae *Spirulina platensis* (Nordst.) Geitl CNM-CB-03, grown in the laboratory of the Institute of Microbiology at the Academy of Sciences of Moldova [72], [73], [74].

It has been suggested that kelp sticks induce the endogenous synthesis of prostaglandins, which contribute to the softening of the cervix due to the release of free arachidonic acid from kelp sticks during their dilation. Biochemical studies of pregnant women’s cervical mucus showed that after using sticks from kelp in the mucus, the activity of elastase, the concentration of interleukin-1 β , interleukin-8, and prostaglandins E_2 and F_2^α significantly increase. In this regard, it is promising and relevant to study the pharmacological effect of biologically active substances of kelp on the maturation of the cervix of the mother in labor and the development of vaginal suppositories for obstetrics [75].

In view of the foregoing, when creating vaginal suppositories with mifepristone and crushed *Laminaria thallus*, 0.01 g of succinic acid was used as a component that has an additional antibacterial and reparative effect per suppository. To reduce the irritating effect of acid on tissues, sodium benzoate, widely used in medicine, was used in the amount of 0.006 g per suppository, which also has an antibacterial effect. Emulsifier T-2 was used as a surfactant in some compositions [76], [77], [78], [79].

For the 1st time, complex experimental studies were carried out to create the composition and rational technology of a new drug in the form of rectal suppositories with a lipophilic extract of bee pollen. The properties of this drug are determined, and methods of quality control and its stability during storage are proposed. For the 1st time, an experimental study of the specific action of the lipophilic extract of bee pollen was carried out: The androgenic effect of this extract and its effect on the sexual behavior of male rats were revealed. In the work Shcheblikina, theoretically and experimentally substantiated the composition and technology of suppositories with a lipophilic extract of pollen, recommended for treating of inflammatory proctological diseases [80].

Conclusion

As the analysis of scientific literature shows, among phytopreparations, a significant place is occupied by preparations based on plant extracts containing a full range of biologically active substances extracted from plants.

When developing technologies for obtaining these natural complexes, it is very promising to use the entire set of biologically active plant substances. Moreover, this is preceded by a search for a promising source – a producing plant, with a complex of biologically active substances for wound-healing and anti-inflammatory action.

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