Reprofiling Hydrogen Peroxide from Antiseptics to Pyolytics: A Narrative Overview of the History of Inventions in Russia

ABSTRACT

Pyolytics are drugs that dissolve thick pus when applied topically. This group of drugs was discovered in early 21st century in Russia as a result of successful repurposing of antiseptics hydrogen peroxide, sodium bicarbonate and sodium chloride from antiseptics to pyolytics. Prior to this watershed event in pharmacy, the problem of effective treatment of purulent diseases had not been solved. The fact is that before that in the treatment of various purulent diseases mainly antiseptics and disinfectants solutions were used, of which hypertonic sodium chloride solution and 3 - 6% hydrogen peroxide solutions took the leading role as "antipurulent" drugs. However, the use of the known antiseptics and disinfectants solutions provided disinfection of the treated surface, but not dissolution of thick pus masses, as the solutions had no effective pyolytic action. Pyolytic activity, i.e. activity of dissolution of thick pus masses, was fantastically increased in hydrogen peroxide solutions only after the possibility of transformation of "old" drugs into "new" drugs by means of artificial changes in physical and chemical properties of their dosage forms was discovered. The greatest (explosive) effect was achieved by developing warm alkaline hydrogen peroxide solutions enriched with oxygen gas under increased pressure. In chronological order, an overview is given of Russian inventions , which formed the basis for the physicochemical repurposing of hydrogen peroxide solutions into pyolytics as well as the basis of temperature and physicochemical pharmacology and pharmaceutics.

Keywords: drugs; search; development; reprofiling; physical-chemical properties; purulent diseases.

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1. INTRODUCTION

Chemotherapeutic, antiseptic and disinfectant solutions are widely used in the treatment of various purulent diseases all over the world [1,2]. Among them the leaders in application are hypertonic solutions of 2 - 10% sodium chloride and solutions of 3 - 6% hydrogen peroxide [3]. The peculiarity of local application of these and some other drugs is that they are injected into the area of long-term non-healing purulent wounds without preheating to body temperature, without prior alkalization and without enrichment with gases [4]. It has been shown that the use of traditional solutions according to the existing medical standards for decades maintained the effectiveness of treatment of long-term non-healing purulent wounds, bedsores and trophic ulcers at the same level [5,6].

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In recent years it has been found out that the validity of local application of standard antiseptic solutions according to standard techniques was reduced only to disinfection of the surface treated with them, but not to urgent dissolution of thick purulent masses and their effective removal outside [7]. The fact is that the arsenal of "antipurulent" drugs was not replenished by drugs with pyolytic activity [8]. Moreover, to increase the effectiveness of treatment of purulent wounds with antiseptic and disinfectant solutions, initially some researchers increased the concentration of ingredients in solutions [9]. However, it was soon discovered that increasing the concentration of ingredients in antiseptic solutions increased their physico-chemical aggressive effect on tissues due to an increase in osmotic activity to excessively high values. It was shown that excessively high hypertonic activity of antiseptics increases their disinfecting effect, but at the same time gives these solutions a pronounced local irritating and even cauterizing effect, which can cause death of granulation tissue and delay the process of wound healing [10,11].

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2. METHODS.

The information contained in the scientific articles was searched using the following online databases: Google Scholar, Scopus, PubMed, Questel-Orbit, Science Direct, Yandex, and E-library. In addition, the information given in the "References" section of the selected scientific articles was analyzed. The information contained in the inventions was searched using Google Patents, EAPATIS, RUPTO, USPTO, Espacenet, PATENTSCOPE, PatSearch, DWPI, and FIIP (RF) databases. Additionally, analogs and prototypes of selected inventions were studied.

The following keywords were used in the search for information: "patent", "invention", "conjunctivitis", "pleurisy", "peritonitis", "arthritis", "panarisis", "abscess", "rhinitis", "tonsilitis", "frontitis", "osteomyelitis", "disease", "wound", "trophic ulcer", "decubitus", "pus", "inflammation", "bronchiectatic disease", "cystic fibrosis", "tuberculosis", "paragonimus", "pulmonary strongyloidosis", "legionary disease", "sputum", "mucus", "pus", "serous fluid", "blood", "catalase enzyme", "treatment", "mucolytics", "expectorants", "pyolytics", "hydrogen peroxide", "sodium bicarbonate", "solution", "antiseptics" and "disinfectants". Information on scientific articles and inventions was searched without year restrictions. The information that was included in the review was limited to drugs, devices, and medical technologies designed for topical application for the emergency dissolution and removal of thick sputum, mucus, pus, serous fluid, and blood clots. The risk of individual bias in the judgments made was reduced by reliance on the substance of the inventions, since it is the substance of the inventions that is the generally accepted criterion of novelty. The analysis performed included 554 inventions, of which the essence of 39 inventions was included to form an overview.

3. RESULTS

Various purulent diseases are reported in many cases to be long-lasting and dangerous [12]. The danger of these diseases is related to the fact that they can cause sepsis and death [13]. Therefore, the dominant view among medical professionals until now is that purulent diseases are dangerous due to microbial contamination of the blood [14]. On this basis, the treatment of various purulent diseases, including septic wounds, trophic ulcers and bedsores, is based on the local application of chemotherapeutic drugs, antiseptics and disinfectants [15]. Antiseptics are most often used in the treatment of septic diseases, of which solutions of 3-6% hydrogen peroxide and hypertonic solutions of 2-10% sodium chloride take the first place [16]. Nevertheless, the effectiveness of these antiseptics in clearing wounds from pus remains low, so the treatment of purulent diseases is often delayed. In this regard, the search for cheap, affordable and more effective "antipurulent" drugs is urgent. However, the traditional way of searching for and developing new drugs is a very expensive, laborious and long process, which, in addition, does not guarantee success at the end of the research conducted [17].

It is reported that In the late 20th century, a new, very cheap and short way to transform "old" drugs into "new" drugs was proposed by purposefully changing the physical and chemical properties of their dosage forms. Initially, this was done by changing the temperature of drug solutions and tissues during local interaction [18]. To prove the prospects of this direction the authors decided to modernize hydrogen peroxide solutions by replacing their acid activity with alkaline activity, increasing the temperature to +37 - +45 °C and gas content, since hydrogen peroxide belongs to popular over-the-counter and cheap antiseptics and is very often used in the treatment of various purulent wounds [19,20].

Today there is every reason to recognize that the chosen path of modernizing hydrogen peroxide solutions turned out to be the right one, as it resulted in the successful repurposing of hydrogen peroxide from antiseptics to pyolytics [20]. The process of hydrogen peroxide modernization (reprofiling) took about 15 years. During the same period of time more than 30 new drugs incorporating hydrogen peroxide were invented in Russia [21]. Most of them are warm alkaline hydrogen peroxide solutions (WAHPSs) [22]. WAHPSs have been reported to consist of the following main ingredients: water, hydrogen peroxide and an alkali (preferably sodium bicarbonate) [20]. Many invented drugs have been shown to be able to dissolve thick masses of pus, blood clots, sulfur plugs, tear stones, mucus, sputum, meconium and other thick biological masses containing the enzyme catalase [23,24]. It has been established that WAHPSs, when locally interacting with sputum, mucus, pus, and serous fluid, are capable of exerting a pyolytic, mucolytic, and antihypoxic oxygen-releasing effect [25-29].

Comment [u4]: Try to include a data quality checker, exclusion and inclusion criteria, and scope, as well as strategies.

Comment [u5]: It is better to include the method of analysis, the limitations, and the way you are trying to minimize the challenge when you are retriving the information from different sources.

The formation of a new direction of search and development of drugs is demonstrated by the chronology of inventions. This can be explained by the fact that all innovative proposals researchers traditionally formalize first in the form of inventions, rather than in the form of scientific articles, since the preliminary open publication of the essence of the created invention excludes obtaining a patent for the invention. We analyzed 561 inventions, of which 44 inventions were used to form an overview. The results of our study showed that more than 30 original hygienic medicines have been invented in recent years for the urgent dissolution, liquefaction and/or bleaching of thick pus, blood clots, stains and crusts, and many other thick or dried biological masses [30]. The vast majority of them were developed in Russia and almost all of them are aimed at hypergaseous, alkaline, hyperosmotic and heating solutions to +37 - +45 °C.

A review of inventions has shown that hydrogen peroxide and sodium bicarbonate have been used to clean surfaces of various objects from various contaminants and for their discoloration in many countries for over 100 years [8,20,21]. However, the first time these ingredients were mixed together to make an alkaline hydrogen peroxide solution was only recently, and it was done in Russia. Other countries continue to use hydrogen peroxide solution with acidic rather than alkaline activity. Because of this, sodium bicarbonate is used, like other alkalis, separately from hydrogen peroxide. Examples of this widespread tradition are inventions for which U.S. patents have been issued, entitled "***Hydrogen peroxide-alkali metal bicarbonate acidic bleaching process***" (US Patent No. 3017236A, 14.08.1959), "***Hydrogen peroxide composition***" (US Patent No. 477438, 12.11.1982), "***Flavor for peroxide-bicarbonate oral compositions***" (US Patent No. 5186926, 03.01.1993) and "**Aqueous disinfecting compositions with rapid bactericidal effect**" (US Patent No. 20030235623, 21.06.2002). The point is that the above inventions propose a hydrogen peroxide solution with acidic properties, i.e. with a pH value of less than 7.0.

Below is a chronology of inventions that formed the basis of physicochemical pharmacology, the formation of the foundations of which allowed to form a general direction of repurposing hydrogen peroxide solutions from antiseptics to pyolytic, mucolytic, hemolytic and expectorant agents. Historical facts show that the development of physicochemical repurposing of drugs began in Russia in 1986. The fact is that it was then that the first patent for the invention "***Method of stopping bleeding***" (RU Patent No. 1263248, 15.10.1986), based on the repurposing of 4% potassium chloride solution into a styptic agent by heating it to +39 - +42 °C, was received. Subsequently, changing the activity of drugs by heating them to a safe level of hyperthermia began to be used more and more often and not only in Russia. Moreover, the foundations of the temperature dependence of pharmacodynamics and pharmacokinetics of drugs (temperature pharmacology) were also laid during this period of time in Russia [31].

The next important step in the development of physico-chemical pharmacology foundations was a patent for the invention "***Method for the treatment of long-term non-healing wounds***" (RU Patent No 2187287, 20.08.2002). The essence of the invention consists in local application of 3% hydrogen peroxide solution and 2-4% sodium chloride solution heated up to +37 °C, after which the purulent wound area is heated up to the development of persistent tissue hyperemia, but not higher than +42 °C.

Then a patent for the "***Floating tablet***" invention was received (RU Patent № 2254121, 20.06.2005). The essence of this invention is to artificially increase the airiness of the tablet by creating in it isolated pores filled with air. The porosity of the tablet and its airiness reduces the given specific weight of the tablet, which makes it possible to repurpose all drugs in tablets from "sinking" to "floating" [32].

After that a very important event was a patent for the invention "***A method of treatment of tuberculous empyema of the pleura according to N.S.Strelkov***" (RU Patent No 2308894, 27.10.2007). The importance of this is related to the fact that euphyllin was first proposed as an "antipurulent" drug (a drug that dissolves thick pus masses). At the same time, it was proposed for the first time to introduce a 24% solution of euphyllin into purulent masses after prior heating it to +42 °C to convert euphyllin from antispasmodics to antiseptics and pyolytics. In this case, a high concentration of the ingredient provided antiseptic properties and high alkaline activity, and hyperthermia potentiated and accelerated the process of alkaline saponification of lipid and protein-lipid complexes that form the basis of purulent masses. In the following years the combination of alkaline activity and local hyperthermia was repeatedly used to develop pyolytic [20].

Then a patent for the invention "***Method of peritoneal dialysis***" (RU Patent No 2336833, 27.10.2008) was received, in which 0.9% sodium chloride isotonic solution was firstly repurposed as an ultrasound contrasting agent due to the preliminary increase of carbon dioxide content under overpressure, which provided visualization of solution flows in a closed abdominal cavity by moving gas bubbles formed during cold boiling.

Practically at the same time there was received a patent for the invention "***Hypergassed and hyperosmotic antiseptic preparation***" (RU Patent No 2331441, 20.08.2008). This remedy is an aqueous antiseptic solution

consisting of 2.7-3.3% hydrogen peroxide, 0.9-10.0% sodium chloride and carbon dioxide to an overpressure of 0.2 ATM at 8°C. The invention provides effective and safe conditions for sanation of purulent wounds, cavities, fistulas, facilitating removal of liquid, viscous and dense biological masses, having a pronounced geyser-like, dehydrating and antiseptic effect.

Also at this time a patent was received for the invention "***Method of uterine lavage***" (RU Patent No. 2327471, 27.06.2008), the essence of which was washing of the uterine cavity with a solution consisting of 0.9% sodium chloride and 3% hydrogen peroxide, heated to +42 - +45 °C.

At the same time a patent for the invention "***Softening agent for thick and viscous pus***" (RU Patent No. 2360685, 10.07.2009) was received. The developed preparation is an aqueous antiseptic solution consisting of 2.7-3.3% hydrogen peroxide and 5.0-10.0% sodium bicarbonate. In it, the peroxide provides a pronounced cold boiling in local interaction with pus, and sodium carbonate provides alkalinity within pH 8.4-8.5 and safe hypertonic activity.

In addition a patent for the invention "***Methods of diagnostics and treatment of clotted hemothorax by AY Malchikov***" (RU Patent No 2368333, 27.09.2009) was received, in which for rapid and reliable dissolution of blood clots local application of solution containing 5% sodium bicarbonate and 1.5% hydrogen peroxide, heated to a temperature of +37 °C was proposed.

The same year a patent was received for the invention "***Method the express remove blood stains from clothes***" (RU Patent No. 2371532, 27.10.2009). This invention proposed a hydrogen peroxide solution with a pH greater than 7.0 and a hypoosmolarity of less than 140 milliosmol/L of water at +26 to +42 °C. At the same time a patent for "***Malchikov's method of removing bile calculus***" (RU Patent No. 2367375, 20.09.2009) was received. In this invention for destruction of gallstones it is proposed to wet them with warm alkaline solution.

A few years later a patent for the invention "***Method and means for removal of sulphur plug***" (RU Patent No. 2468776, 27.06.2012) was received. The essence of the present invention is that a solution of 0.3-0.5% hydrogen peroxide and 1.7-2.3% sodium bicarbonate heated to +42 °C is injected into a sulfur plug pricking to complete plug infiltration.

At the same time a patent for the invention "***Agent for fistula sanitation in infected pancrenecrosis***" was received. (RU Panent No. 2455010, 10.06.2012). The invented drug has special physical and chemical properties that provide inhibition of pancreatic enzymes.

A little later a patent for the invention "***E.M.Soikher's hyperoxygenated agent for venous oxygen saturation***" (RU Patent No. 2538662, 10.01.2015). The essence of this invention is that the invented drug is an aqueous solution consisting of 0.85% sodium chloride, 0.10% sodium bicarbonate and 0.05-0.29% hydrogen peroxide. The unique formulation provides catalase breakdown of hydrogen peroxide without the formation of gas bubbles, which eliminates blood vessel embolism.

In the same year was received a patent for the invention "***Method of maintenance of live fish during transportation and storage***" (RU Patent No. 2563151, 20.09.2015). The essence of this invention is the introduction of hydrogen peroxide solution into the water with live fish instead of oxygen.

In parallel, a patent for the invention "***Bleach bruising***" (RU Patent No. 2539380, 20.01.2015) was received. The essence of this invention is that a solution for intradermal injections was proposed that contains sodium bicarbonate, hydrogen peroxide, EDTA-Na_2 and water.

In the following year, several patents were obtained for inventions intended for bleaching blood spots: "***Bleaching agent***" (RU Patent No. 2589682, 10.07.2016), "***Method for skin bleaching in the bruise area***" (RU Patent No. 2586278, 10.06.2016), "***Agent for intradermal bleaching of bruises***" (RU Patent No. 2573382, 20.01.2016), "***Method for skin bleaching in the bruise area***" (RU Patent No. 2582215, 20.04.2016), "***Agent for increasing resistance to hypoxia***" (RU Patent No. 2604129, 10.12.2016) and "***Lymphosubstrate for local maintenance of organ and tissue viability under hypoxia and ischemia***" (RU Patent No. 2586292, 10.06.2016). The essence of all these inventions is the use of a warm alkaline hydrogen peroxide solution, which provides the release of gaseous oxygen, but excludes vascular gas embolism.

The following year, a patent for the invention "***Means for increasing physical endurance***" (RU Patent No. 2634271, 24.10.2017) was obtained. The invention is that drinking water includes 7% glucose, 3% hydrogen peroxide and oxygen gas to create an overpressure of 0.2 ATM at +8°C. In addition, this year a patent was received for the invention "***Energy drink***" (RU Patent No. 2639493, 21.12.2017), intended for enteral feeding of children, made as a sterile solution including glucose, ethyl alcohol, 0,3-0,5% hydrogen peroxide, citric acid, prepared water for injection, containing oxygen gas under excess pressure 0,2 ATM at +8° C. Also this year, a patent for the invention "***Carbonated mouthwash***" (RU Patent No. 2635992, 17.11.2017), which includes

sodium chloride, sodium hydrophosphate, sodium dihydrophosphate, hydrogen peroxide, water and helium gas to create 0.2 ATM overpressure at +8°C was obtained.

At the same time a patent for the invention "***Method for emergency bleaching and blood crust removal from skin in place of squeezed out acne***" (RU Patent No. 2631593, 25.09.2017), which includes the use of a solution of 3% hydrogen peroxide and 10% sodium bicarbonate was received. Additionally, patents for the inventions "***Method for whitening of hematoma under nail***" (RU Patent No. 2631592, 25.09.2017), "***Method for whitening of bruise under eye***" (RU Patent No. 2639283, 20.12.2017) and "***Means for intravital skin whitening near blue eyes***" (RU Patent No. 2639485, 21.12.2017), which included the local use of a bleach solution at a temperature of +37 - +42 °C, i.e. the use of WAHPSs.

The following year, a patent was obtained for the invention "***Bleach bleacher for soaking bandages stuck to the wound***" (RU Patent No. 2653465, 08.05.2018), which contains 0.75-1% hydrogen peroxide, 1.2% sodium bicarbonate, 0.5% lidocaine hydrochloride and bidistilled water. The use of the invention provides optimal osmotic, alkaline, buffering, foaming, detergent, anesthetic and bleaching activity of the solution required in wound sanitation for effective and safe softening of the bandage, bloodless and painless removal from the wound and bleaching of the wound and skin around it under surface anesthesia.

In the same year the patents for the inventions "***Decolorant of blood***" (RU Patent 2647371, 15.03.2018) and "***Bleaching cleaner of dentures***" (RU Patent No. 2659952, 04.07.2018) were received. The essence of these inventions is that a solution including 3 ± 0.3% hydrogen peroxide and sodium bicarbonate in an amount ensuring saturation of the solution and preservation of the residue at +42 °C has been proposed to be used as a bleaching agent of blood at skin and textile surfaces. In turn, a solution of 2.0-10.0% sodium bicarbonate and 3±0.3% hydrogen peroxide, which was enriched with oxygen gas at an overpressure of 0.2 ATM at +8°C was proposed for the whitening of dentures. Moreover, it was suggested that the solution be heated to a temperature of +37 - +42 °C before use.

The following year, a patent for the invention "***Method of emergency bleaching of skin hematoma under eye***" (RU Patent No. 2679334, 07.02.2019) was obtained, in which a solution of 3% hydrogen peroxide and 10% sodium bicarbonate at a temperature of +37 - +42 °C was proposed for bleaching.

Then a patent was obtained for the invention "***Method of using a solution to remove plaque with an irrigator***" (RU Patent No. 2723138, 09.06.2020). In this invention, a solution of 2.0-10.0% sodium bicarbonate and 2.7-3.3% hydrogen peroxide, which was additionally increase gas argon content at an equilibrium pressure of 3-4 ATM, was first proposed for plaque removal with an irrigator. Moreover, the solution after carbonation was recommended to be stored in a hermetically sealed container and heated to a temperature of +43 to +65 °C before use.

In the same year the patents for the inventions "***Gel for children's skin***" (RU Patent No. 2713943, 11.02.2020) and "***Peeling agent for foot hyperkeratosis***" (RU Patent No. 2730451, 24.08.2020) were received. The essence of the invented gel is that it is used heated to +45 °C, consists of water, 0,75-1% hydrogen peroxide, 2% lidocaine hydrochloride and cationic surface-active substances in the amount ensuring gel-like consistency at temperature +24-+26 °C, and has alkaline activity with pH value of 8,0-8,5. The essence of the second hygienic preparation is that it is a hypertonic alkaline solution of 3.0-5.0% potassium hydroxide and 0.5-20.0% hydrogen peroxide at pH 13.0-14.0 and osmotic activity 350-560 mosmol/l water heated to +38 - +42 ° C, enriched with oxygen gas to create overpressure of 0.2 ATM. at +8 ° C.

In 2022 a patent for the invention "***Dandelion milky juice stains bleaching agent***" (RU Patent No. 2765469, 31.01.2022) was received. The bleaching agent relates to household detergents, in particular stain removers, and is intended for urgent dissolution, discoloration and removal of stains of thickened and darkened milky juice of dandelion and other rubbery plants on white clothes. The product is a liquid stain remover consisting of 2 to 4 parts of a solution of 3% hydrogen peroxide and 0.1% detergent, 1 part of a solution of 10% ammonia alcohol and 3 parts of nefras consisting of equal amounts of white spirit and gasoline Kalosha.

In the same year was received a patent for the invention "***Glass washing liquid***" (RU Patent No. 2763882, 11.01.2022). This glass washer is an aqueous solution containing 0.06-0.5% hydrogen peroxide, 0.1% colorless detergent and 0.08-0.1% ammonia alcohol. Such composition indicates that this glass washer is a variant of alkaline hydrogen peroxide solution. Due to this it provides emergency loosening, softening, discoloration of particles of dung, manure, residuals of insects bodies, turning them into foam of white color, their urgent removal from the surface of the windshield of the vehicle.

An analysis of the essence of these inventions was performed. The results of the analysis show that all the drugs invented in Russia are solutions that include hydrogen peroxide, sodium bicarbonate and/or sodium chloride and have unique physical and chemical properties [20]. All the above solutions have a nonspecific

local action provided by local hyperthermia, moderate alkalinity, osmotic activity, on the one hand, and the enzyme catalase contained in pus masses and other biological tissues, on the other hand. As a result of local application, all alkaline hydrogen peroxide solutions quickly turn these masses into a fluffy white oxygenated foam [22,23,25]. This has been shown to occur due to alkaline saponification of lipid and protein-lipid complexes and a cold boiling process caused by the formation of gas bubbles due to catalase splitting of hydrogen peroxide into oxygen gas and water and/or due to a decrease in the initial overpressure [33,34].
The large number and variety of Russian inventions clearly testify to the continuing progress of WAHPSs development in Russia. In particular, it is reported that ***aerosols for treatment of respiratory obstruction*** in purulent obstructive bronchitis (RU patent No. 2735502, 03.11.2020) and for optimization of artificial mechanical ventilation in case of airway obstruction by thick sputum, mucus and pus in the final stage of non-specific bilateral pneumonia in COVID-19 (RU patent No. 2742505, 08.02.2021) were recently invented in Russia [35]. Moreover, these drugs are based on WAHPSs.

DISCUSSION

The present review has shown that many purulent diseases have a long lasting character despite the use of the most modern medicinal "antipurulent" drugs [12]. It has been shown that in the treatment of various purulent diseases the antiseptics are the leaders among the drugs, and among them are hypertonic solutions of 2 - 10% sodium chloride and solutions of 3 - 6% hydrogen peroxide [36-38]. It has been shown that in the treatment of long-term non-healing purulent wounds these antiseptics are used in accordance with the medical standard, which allows local application of antiseptic solutions at room temperature and with a pH value less than 7.0, that is, with acidic activity [39-41]. At the same time, it was found that cooling from +37 to +25 °C and decrease of pH below 7.0 compacts the colloidal masses. [42]. It was also shown that the injection of cold and acidic solutions of known antiseptics into the area of purulent wounds provides disinfection of the treated surface, but does not dissolve and remove thick and viscous pus [20,43]. It has been reported that the use of known antiseptic solutions according to current medical standards does not provide effective and rapid dissolution and removal of thick and sticky pus in the treatment of long-term non-healing purulent wounds, bedsores and trophic ulcers [44]. It has been established that the reason for the low effectiveness of traditional treatment of bedsores, trophic ulcers and many other purulent diseases, including COVID-19, is the absence of pyolytics in the medical standards of treatment of these diseases [7,20,41].
It has been shown that the microbiological composition of pus has been well studied, but physical, chemical, physico-chemical and biochemical properties of thick and viscous pus masses in various purulent diseases have not been adequately studied [45,46]. In addition, the mechanisms of local action of antiseptic and disinfectant solutions with purulent masses remain insufficiently studied [43]. Lack of the above information explains why modern medical technologies for treatment of long-term non-healing purulent wounds do not provide fast and effective dissolution of dense pus and its removal outward, in particular in tuberculous empyema of the pleura and purulent airway obstruction in COVID-19 [47]. It has been reported that known mucolytic and expectorant drugs also do not provide high speed and efficiency in dissolving and removing thick and sticky pus in various purulent diseases [48]. All this justifies the need to search for new and more effective "antipurulent" drugs [49].
It is shown that in 1986 in Russia the first patent for the invention was received, the essence of which consists in irrigation of the bleeding surface with a repurposed drug, namely - a solution of 4% potassium chloride, but not cold, but heated to a temperature of +39 - +42 ° C. The fact is that a solution of 4% potassium chloride at +39-+42 C has different physical and chemical properties than at room temperature. In particular, local application of a warm solution of 4% potassium chloride causes hyperkaline spasm (contracture) of blood vessels, which helps to stop bleeding. Therefore, safe hyperthermia of the drug solution became the basis for the repurposing of potassium chloride from the pharmacological group "Macro- and microelements" to the group "Blood-stopping drugs". These facts indicate that in this period of history of the development of pharmacology the foundations of temperature pharmacology, temperature conversion of drugs, physical and chemical material science and pharmacy were laid. And it happened in Russia.
A review of the inventions has shown that to date, more than 30 fundamentally new drugs have been invented that differ from all known drugs by their unique physical and chemical properties. The basis of the majority of the invented drugs are warm alkaline hydrogen peroxide solutions (WAHPSs) [8,19,22].
Since such studies are still in their infancy, the main information about them is not found in scientific articles, but in inventions. Therefore, the review presented was based on descriptions of those inventions in which hydrogen peroxide was used. The emphasis was placed on hydrogen peroxide because it is hydrogen peroxide that can urgently decompose into water and molecular oxygen under the influence of the pus mass catalase enzyme. In addition, hydrogen peroxide is an available and over-the-counter medication [50,51].
A total of 561 inventions were analyzed, of which 44 inventions were used to form an overview because only they included hydrogen peroxide and/or were intended for local application for the purpose of dissolving thick colloidal masses containing catalase. Of these, 40 inventions were created in Russia.

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The analysis of the contents of the above inventions demonstrated that at the beginning of the 21st century more than 30 drugs were invented in Russia, marking the beginning of hydrogen peroxide re-profiling from antiseptics to pyolytic by purposefully replacing the acid activity of the solutions with alkaline activity within pH 8.4-8.5, heating them to +37 - +45 °C, ensuring isotonic activity and increasing the content of dissolved gases.

It was found that WAHPSs in a single local interaction with pus masses and many other colloidal biological tissues containing the enzyme catalase, very quickly turn them into a fluffy white oxygen foam [19,22]. It was found that when applied topically, WAHPSs have the following effect on pus: they dissolve pus masses due to alkaline saponification of lipid and protein-lipid complexes and simultaneously turn pus into a fluffy foam due to the rapid formation of gas bubbles in the process of cold boiling [8,20,22]. It has been shown that the cold boiling process can be realized by catalase splitting of hydrogen peroxide into water and molecular oxygen, as well as by initially increasing the gas content (oxygen or other gas) in the solution by means of excess pressure [23]. Moreover, it was in Russia that for the first time in the world it was proposed to increase the gas content in antiseptic solutions by creating excess pressure in them and thus turn known medicinal solutions into carbonated solutions with a new mechanism of action and with a new indication for use [4,52,53]. The enrichment of alkaline hydrogen peroxide solutions with oxygen gas or other gases has been shown to increase the pyolytic activity [23]. In addition, local application of WAHPSs has been reported to discolor the skin and nail plate in the area of hematoma and/or bruise, as well as to whiten teeth, dental and ceramic products [8,24,30].

Consequently, the above data indicate the prospects of repurposing hydrogen peroxide from antiseptics to pyolytics due to a targeted change in the physical and chemical properties. It is shown that the advantage and simultaneously the limitation of hydrogen peroxide reprofiling from antiseptics into pyolytics is the local application of drugs and non-specific pharmacological activity due to the original physical and chemical properties of the drugs. The above results convince of the need for further research on the use of targeted changes in the physicochemical properties of hydrogen peroxide for its repurposing from antiseptics to pyolytics. Therefore, it is hoped that more information on the advantages and disadvantages of hydrogen peroxide solutions and other antiseptics with modified physico-chemical properties will be obtained in the future.

3. CONCLUSION

Thus, in the late 20th and early 21st centuries in Russia completely new medicines were invented, consisting of "old" medicines, but in new combinations and with new, unique physical and chemical properties, providing a new mechanism of action in local interaction with pus. It is shown that the drugs of this group are warm alkaline solutions of hydrogen peroxide, which in local interaction with pus masses urgently turn them into a fluffy oxygen foam of white color and due to this clean pus wounds from pathological biological masses and increase the oxygen content in the tissues. Due to this mechanism of local action, warm alkaline solutions of hydrogen peroxide antiseptic are called "Pyolytics" or "Pus Dissolvers".

It has been established that the mechanism of action of pyolytic agents, which are warm alkaline solutions of hydrogen peroxide, is provided, on the one hand, by hyperthermia and alkalinity and, on the other hand, by the presence of catalase enzyme in the purulent masses. The main ingredients of the pyolytic formulations developed for the first time in Russia are indicated. Inventions are listed in chronological order, which allowed to purposefully change physical and chemical properties of hydrogen peroxide solutions, thanks to which hydrogen peroxide has been successfully repurposed from antiseptics to pyolytic. The results obtained give hope for the expansion of the arsenal of "antipurulent" drugs in the near future by including warm alkaline hydrogen peroxide solutions in the role of piolytics.

Comment [u7]: Try to infer the recommendation from the point of view of your results.

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