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SYSTEMATIC-REVIEW ARTICLE

Catalase: A Potential Pharmacologic Target for Hydrogen Peroxide in the Treatment of COVID-19

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Abstract: ***Background*:** Acute respiratory distress syndrome in the elderly with COVID-19 complicated by airway obstruction with sputum and mucus, and cases of asphyxia with blood, serous fluid, pus, or meconium in newborns and people of different ages can sometimes cause hypoxemia and death from hypoxic damage to brain cells, because the medical standard does not include intrapulmonary injections of oxygen-producing solutions. The physical-chemical repurposing of hydrogen peroxide from an antiseptic to an oxygen-producing antihypoxant offers hope for the development of new drugs.

***Methods*:** This manuscript is a meta-analysis performed according to PRISMA guidelines.

***Results*:** It is shown that replacement of the traditional acidic activity of hydrogen peroxide solutions by alkaline activity with pH 8.4 and heating the solutions to the temperature of +37 - +42 °C allows to repurpose hydrogen peroxide from antiseptics into inhalation and intrapulmonary mucolytics, pyolytics and antihypoxants releasing oxygen. The fact is that warm alkaline hydrogen peroxide solution (WAHPS) in local interaction with sputum, mucus, pus, blood and meconium provides optimal conditions for the metabolism of hydrogen peroxide to oxygen gas under the action of the enzyme catalase, always present in these tissues. It was established that WAHPS liquefies these biological masses due to alkaline saponification of lipid and protein-lipid complexes and simultaneously transforms dense masses into soft oxygen foam due to active enzymatic metabolism of hydrogen peroxide to oxygen gas, the rapidly appearing bubbles of which are formed by the type of "cold boiling" and literally explode these masses. The results of the first experiments showed that inhalation and intrapulmonary injections of WAHPS can significantly optimize the treatment of suffocation and hypoxemia.

***Discussion*:** The results showed that catalase, which is found in sputum, mucus, pus, and blood, may be a target for localized WAHPS because this enzyme provides an intensive metabolism of hydrogen peroxide to oxygen gas up to the formation of the cold boiling process.

***Conclusion*:** These data provide a new perspective way for intrapulmonary drugs and new technologies for the emergency increase of blood oxygenation through the lungs in asphyxia with thick sputum, mucus, pus, meconium and blood.

Keywords: Hydrogen peroxide, catalase, oxygen-producing antihypoxant, pyolytics, mucolytics, hemolytics, expectorants, intra-pulmonary, suffocation, hypoxia.

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1. INTRODUCTION

It is no secret that severe bilateral nonspecific pneumonia, which develops in COVID-19 in elderly and senile people, is the leading mortality factor in new coronavirus infection [1-5]. The point is that subtotal and total inflammation of lung tissue in this disease often becomes the cause of hypoxemia development [6-10]. In turn, the true cause of biological death in patients with new coronavirus infection is hypoxic damage in brain cells [11-15].

It has been reported that severe bilateral nonspecific pneumonia in COVID-19 is characterized by inflammation of the peripheral regions of the lungs, decreased airway lumen and airflow in them [16-20]. It is shown that lung airflow is reduced due to mechanical compression of airways by lung tissue, as its volume increases due to the edema that develops in this pneumonia [21, 22]. In this regard, it becomes clear that the absence of air in the airways stops their "ventilation" with air and the removal of sputum and mucus from them with air to the outside [23-26]. In addition, cessation of ventilation of respiratory tracts promotes accumulation in not only sputum and mucus, but also pus, because nonspecific pneumonia in elderly and senile people is often combined with purulent bronchitis, which becomes the cause of pus accumulation in bronchi and bronchioles [27, 28]. Sometimes blood streaks are added to these colloidal fluids [29-35].

It has been shown that severe nonspecific bilateral pneumonia in COVID-19, which develops in elderly and senile patients, is difficult to treat largely due to the loss of airway airflow [36-39]. The fact is that the lack of ventilation of the respiratory tract contributes to the accumulation of oxygen-free colloidal fluids in them, the excess of which closes the vicious circle of development of suffocation and hypoxia, as thick sputum, mucus and pus further reduce the lumen of the airways and become an additional mechanical obstacle to the movement of air to the alveoli [40-45]. This reduces the effectiveness of treatment of nonspecific pneumonia with chemotherapy and anti-inflammatory drugs [46, 47], as well as the effectiveness of eliminating hypoxemia with oxygen therapy [48, 49]. The latter is the most important, as hypoxemia is the direct cause of high mortality of patients in the final stage of severe nonspecific bilateral pneumonia [11, 27, 40, 50]. That is why in the critical situation in the final stage of nonspecific bilateral pneumonia in COVID-19 all patients are administered intermittent mandatory ventilation with breathing gas enriched with oxygen [11, 27, 40, 44-53].

At the same time, the standard of medical care for severe hypoxia caused by obstruction of bronchi and bronchioles by sputum, mucus and pus in COVID-19 does not include drugs that provide urgent recanalization of airways [11, 40, 50, 51, 54]. In particular, the standard of medical care does not include intrapulmonary warm alkaline hydrogen peroxide solutions (WAHPSs), which at local interaction with sputum, mucus and pus can urgently convert them into oxygen foam [27, 40, 50, 51]. Under these conditions, the use of traditional drugs does not provide elimination of suffocation and hypoxemia. Moreover, respiratory obstruction may increase despite treatment. Therefore, the peripheral parts of the lungs may completely lose airiness, and the airways in them may be completely deprived of their lumen due to their compression by the surrounding inflamed lung tissue and lumen closure by inflamed mucous membranes and colloidal fluid accumulation. This may make coughing and sneezing impossible. Therefore, the natural restoration of airway patency with the help of airflow during coughing and sneezing is often completely excluded [55, 56].

Persistent respiratory obstruction reduces the efficiency of blood oxygenation through the lungs not only during natural breathing but also during forced mechanical ventilation with oxygen [48, 49, 52, 53, 57-61]. In these conditions, it is possible to normalize blood oxygenation and save patients' lives only with the help of extracorporeal membrane oxygenation (ECMO) [62-67]. However, ECMO is unaffordable for most patients, and the technology itself is very dangerous for patients' health and increases the cost of COVID-19 treatment many times [68-75]. That is why new drugs and new therapies are urgently needed that can provide immediate replacement of oxygen-free colloidal fluids with gaseous oxygen in the airways of peripheral lung regions to become a worthy alternative to ECMO.

To prevent and treat novel coronavirus infection, research groups around the world are developing vaccines, drugs and immunobiologic compounds. However, producing sufficient vaccine doses for the entire population and SARS--CoV-2 variants is a challenge for the pharmaceutical industry. In turn, finding and developing new drugs in the traditional way, namely by screening thousands of new chemical compounds, is a very time-consuming, costly and inefficient endeavor. Under these circumstances, one of the promising areas of new drug discovery and development could be the repurposing of known drugs, the development of mononuclear antibodies, reconstituted plasma and mesenchymal stem cells to control viral infection/replication or hyperinflammatory response to a novel coronavirus [76].

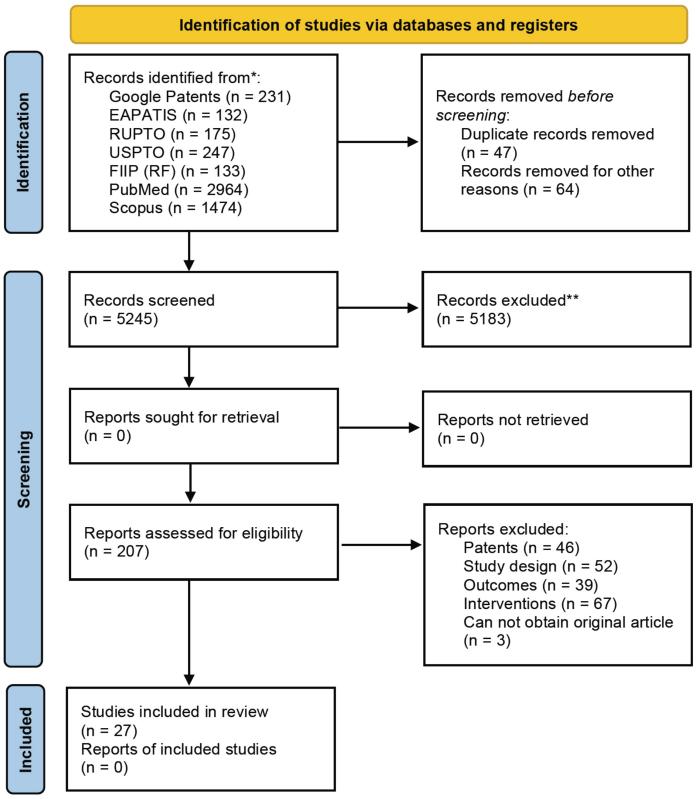
2. MATERIALS AND METHODS

We analyzed the data available in the literature on the role, on the one hand, of sputum, mucus and pus in the airways in the formation of acute respiratory distress syndrome (ARDS) and hypoxemia in severe acute respiratory syndrome (SARS) in patients with COVID-19 and, on the other hand, of warm alkaline hydrogen peroxide solutions (WAHPSs) inside the airways in the oxygenation of these colloidal fluids and circulating blood during acute hypoxia. Various purulent masses, donor blood, blood clots, blood stains, sulfur plugs, tear stones, meconium, sputum, pus and mucus from the respiratory tracts of humans and warm-blooded animals, as well as especial artificial sputum containing the enzyme catalase, were used as biological objects of comparison. The fact is that the listed colloidal fluids and colloidal fluids accumulating in the respiratory tract during respiratory obstruction in patients with COVID-19 have similar physico-chemical and biochemical properties that deter-

mine the outcome of local interaction with hydrogen peroxide. It is a well-known fact that hydrogen peroxide undergoes catalase transformation into oxygen and water. The screening was carried out with special attention to the possibility of making appropriate analogies between drugs and colloidal fluids in various parts of the body and model conditions, on the one hand, and in the respiratory tract with respiratory obstruction, on the other hand. No time limits were chosen for the study, and all types of articles were included, as well as descriptions of inventions in English and Russian.

Information contained in inventions and scientific articles was used. The information contained in the description of inventions was searched using the following databases: Google Patents, EAPATIS, RUPTO, USPTO, Espacenet, PATENTSCOPE, PatSearch, DWPI and FIIP (RF). In addition, analogues and prototypes indicated in the selected inventions were studied. The information contained in the scientific articles was searched using the following databases: Index Copernicus, Google Scholar, Crossref, Web of Science, Scopus, PubMed, Questel-Orbit, Science Direct, Yandex, and E-library. In addition, the information in the "References" section of the selected scientific articles was studied.

The following keywords were used in the search for information: "COVID-19", "SARS-Cov-2", "MERS", "coronavirus", "lungs", "pneumonia", "bronchitis", "disease", "treatment", "inflammation", "airways", "bronchi", "bronchioles", "alveoli", "mucous membrane", "respiratory obstruction", "ARDS", "sputum", "mucus", "pus", "serous fluid", "blood", "catalase enzyme", "hypoxia", "oxygen", "saturation", "air", "aerosol", "inhalation", "intrapulmonary", "bronchodilators", "mucolytics", "pyolytics", "drugs", "corticosteroids", "antihistamines", "hydrogen peroxide", "sodium bicarbonate", "solution", "antiseptics", "disinfectants", "expectorants", "chemotherapy", "oxygen therapy", "artificial ventilation", "ECMO", "cost", "warm alkaline hydrogen peroxide solution", "WAHPS", "patent", "invention" and "death". Information on scientific articles and inventions was searched with no year restrictions. A systematic review was conducted according to the quality standards described in the AMSTAR measurement tool and the PRISMA 2009 checklist [77, 78]. The search strategy was based



PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.
*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: http://www.prisma-statement.org/

on the PICO model [79, 80]. Co-authors independently selected, evaluated, and extracted data from scientific articles and invention descriptions. Inconsistencies in reviews were resolved by consensus. The block diagram for article selection was a spiral in which each turn of the spiral was an iteration [81, 82].

The review included information on drugs, devices and medical technologies that may be suitable for emergency oxygenation of serous fluid, thick sputum, mucus, pus, meconium and/or blood within the respiratory tract and increasing blood oxygenation through the lungs. The following criteria were used to exclude information from the review: unsuitability for administration into edematous lung tissue and/or obstructed airways for immediate oxygenation of serous fluid, thick sputum, mucus, pus, lymph, blood and/or meconium in the airways, and lack of absolute worldwide novelty

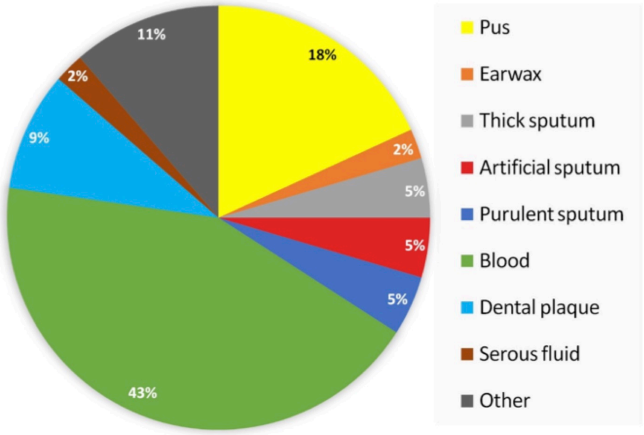


Fig. (1). Inventions according to their intended effects on biological objects. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

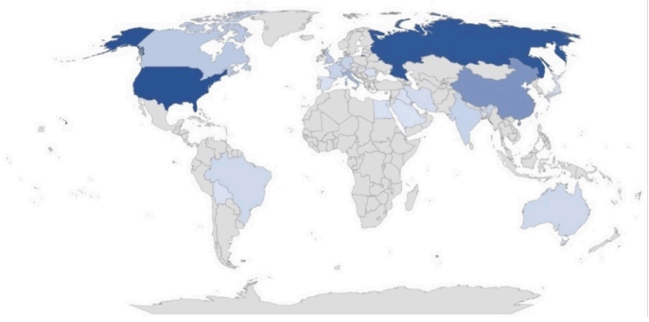


Fig. (2). Geography of articles. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

and/or patent on the invention. To reduce the risk of individual bias in our judgments, we relied on the substance of the inventions rather than the substance of the scientific articles. The fact is that it is the essence of inventions that is the generally accepted criterion of absolute world novelty. The content of 571 inventions was analyzed, of which the essence of 46 inventions was used for the review (Fig. **1**). In addition to inventions, the content of 148 articles was analyzed (Figs. **2** and **3**). Disagreements that arose among co-authors when discussing inventions and articles were resolved with the help of third (external) collaborators.

3. RESULTS

Coronavirus 2019 (COVID-19) adults older than 65 years of age have been found to account for 80% of hospitalizations and have a 23 times higher risk of death than people under 65 years of age [1, 83, 84]. Clinically, patients with COVID-19 most commonly present with fever, cough, and dyspnea, after which the disease may progress to acute respiratory distress syndrome, pulmonary consolidation, cytokine release syndrome, endotheliitis, coagulopathy, multi-organ failure, and death [85]. Co-morbidities such as cardiovascular disease, diabetes and obesity increase the likelihood of mortality, but they alone do not explain why age is an independent risk factor [1, 36, 85]. At the same time, there are reports that the high mortality of elderly patients with COVID-19 may be related to the presence of thicker and more viscous sputum and the difficulty in removing it from the airways [86]. In addition, purulent bronchitis may be attached [87].

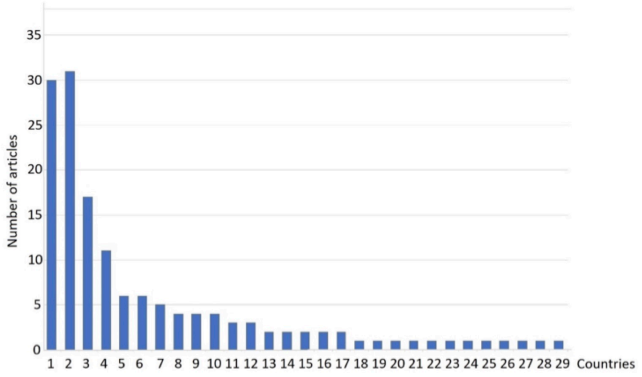


Fig. (3). Country distribution of articles. 1- Russia, 2 - USA, 3 -China, 4 - Italy, 5 - UK, 6 - Canada, 7 - International Team, 8 - France, 9 - Germany, 10 - India, 11 - Australia, 12 - Brazilia, 13 - Belgium, 14 - Iran, 15 - Japan, 16 - Taiwan, 17 - Denmark, 18 - Bolivia, 19 - Romania, 20 - Dominica, 21 - Republic Korea, 22 - Switzerland, 23 - Netherland, 24 - Croatia, 25 - Spain, 26 - Iraq, 27 - Egypt, 28 - Saudi Arabia, 29 - Slovak Republic. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

3.1. Coronavirus Disease 2019 as a Type of Suppurative Bronchitis

In patients infected with SARS-CoV-2, cytokine storm is thought to play an important role in the pathogenesis of severe manifestations of COVID-19 such as acute respiratory distress syndrome, thromboembolic diseases (acute ischemic strokes caused by large vessel occlusion and myocardial infarction, encephalitis, acute kidney injury), and vasculitis (Kawasaki syndrome in children and renal vasculitis in adults). Therefore, consideration of the cytokine storm and the use of anti-inflammatory therapies to target it in COVID-19

patients may alleviate the symptoms of the disease and improve the outcomes of COVID-19 patients, especially in high-risk cases of severe disease [88, 89]. However, the pathogenesis of hypoxemia in new coronavirus infection is of a special nature, so traditional anti-inflammatory drugs do not eliminate COVID-19 suffocation and hypoxemia [7-10].

It has been suggested that coronavirus disease is a variant of suppurative bronchitis [29]. According to the authors, this is indicated by the fact that the COVID-19 outbreak in the form of a respiratory infection epidemic occurs at the time of year when influenza epidemics are most prevalent. In addition, the above assumption proves that influenza bacillus is almost always present in the sputum and pus of affected bronchioles in patients with COVID-19. Unlike normal cases of bronchitis, patients with COVID-19 have characteristic sputum, complete occlusion of small bronchi and bronchioles with thick pus, absence of air in bronchi and bronchioles, marked purulent bronchitis, cyanosis, severe tachycardia, fever (especially before death), and extremely high mortality. The above assumption is indirectly supported by the fact that the best results of treatment of patients with COVID-19 were obtained when using a steam tent and similar physiotherapeutic methods of treatment [29, 86, 90]. At the same time, it is well known that the steam tent, ancient method of physiotherapy, which is an analogue of the Turkish bath hammam, is effective in the treatment of purulent bronchitis, because water steam liquefies thick and sticky phlegm and pus and facilitates their expectoration [91, 92]. In addition, it was reported that elderly patients with COVID-19 had concomitant lymphopenia or an increased number of neutrophils, and in the group in critical condition, the proportion of patients with grade 3 sticky sputum was higher than in the group of non-critical patients [90, 93]. Based on this, the authors suggested that changes in sputum characteristics may be one of the early warning signs of critical COVID-19.

The role of purulent bronchitis as an important factor in coronavirus disease proves that the use of high-dose ambroxol and drainage in the supine position was relatively high in patients with COVID-19 with good prognosis [86]. For this reason, it is hypothesized that early use of high-dose expectorants and airway drainage in the supine position in patients with COVID-19 can prevent progression to critical disease and improve the prognosis of critically ill patients [86, 90].

Other authors draw the attention of researchers to the ability of human coronaviruses to survive in the environment and to the high efficacy of known antiseptic-disinfectants against them [94]. The prospect of antiseptics in the treatment of patients with severe COVID-19 is also proved by the fact that the viral load of sputum filling the lower respiratory tract is closely associated with the risk of progression and severity of COVID-19 [95]. This explains the efficacy of antiviral treatment of influenza and the possible inhibition of viral disease progression and mortality in influenza [96]. However, clinical results of treatment of patients with COVID-19 do not confirm the high efficiency of traditional antiviral drugs [97, 98]. This paradox has not yet been explained. At the same time, clinical results of treatment of patients with new coronavirus disease indicate the effectiveness of steam tent, hamam, high-dose expectorants and airway drainage in the supine position of patients. In all likelihood, this is primarily relevant in the presence of thick sputum, mucus and pus in the respiratory tract, primarily in patients over 65 years of age.

3.2. Thick Sputum, Mucus and Pus in the Airways as Factors of Airway Obstruction in COVID-19

Consequently, COVID-19 may be accompanied by purulent bronchitis. Therefore, the accumulation of thick sputum, mucus and purulent masses in the airways of patients may be one of the important factors of respiratory obstruction [11, 27]. This explains why not only antiviral but also mucolytic and pyolytic therapy is important to prevent lethal outcomes in severe COVID-19 patients [40]. The importance of pyolytics and mucolytics in the treatment of purulent bronchitis in COVID-19 is explained by the fact that complete blockage of small bronchi and bronchioles with thick sputum, mucus and pus and deprivation of airways become the cause of hypoxemia. In turn, the prolonged persistence of hypoxemia becomes the cause of hypoxic brain cell damage and death of patients [11, 40, 50, 99]. At the same time, known antiseptics and disinfectants have antiviral action, but do not have effective mucolytic and pyolytic action [27, 40, 51].

Thus, known antiviral, antiseptic and disinfectants are suitable for emergency eradication of the virus, but are not suitable for emergency liquefaction and removal of thick sputum, mucus and pus from the respiratory tract. Therefore, known antiviral agents, antiseptics and disinfectants do not provide emergency removal of these colloidal masses from the respiratory tract, do not restore the patency of the respiratory tract for inhaled gases, do not eliminate hypoxemia and do not prevent death in severe patients with COVID-19 [27, 100]. In turn, among the known expectorants, mucolytics and mucokinetics, there are also no drugs that provide immediate removal of thick sputum, mucus and pus from the respiratory tract while simultaneously releasing oxygen gas [101, 102]. Unfortunately, there are no generally recognized drugs with such pharmacological activity. Therefore, in nonspecific 2-sided pneumonia in the final stage of COVID-19, thick pus, mucus, and sputum clogging the airways remain the most difficult obstacle to effective ventilation and delivery of oxygen to the blood through the alveoli to eliminate hypoxemia. Therefore, thick sputum, mucus and pus in purulent bronchitis in COVID-19 remain important factors not only in airway obstruction but also in hypoxemia.

The reason for the accumulation of thick sputum, mucus and pus in the respiratory tract is the high viscosity and stickiness of these colloidal masses. This makes it very difficult to remove them from the respiratory tract by coughing, sneezing, and known expectorant, mucolytic and mucokinetic drugs, which allows the participation of these masses in the development of respiratory obstruction and hypoxemia in the final stage of COVID-19 [40, 50]. The fact is that th-

ese colloidal masses have not been previously considered as a target for pharmacological screening of new drugs in the search and development of drugs that dissolve them immediately with a single application [100]. Unfortunately, many researchers and clinicians believe that one of the leading causes of hypoxia that develops in patients with severe COVID-19 is respiratory obstruction, which is caused by airway mucosal edema of an allergic nature, much like a severe bronchial asthma attack [103]. Therefore, the use of inhaled corticosteroids is still the mainstay of treatment for patients with severe COVID-19 [41, 104-106]. However, the clinical efficacy of inhaled corticosteroids remains low in severe COVID-19 and insufficiently high in severe asthma attacks. At the same time, it has been shown that one of the reserves for increasing the effectiveness of inhaled corticosteroids in bronchial asthma and COVID-19 is their combination with inhalation of warm aqueous solutions of hydrogen peroxide and sodium bicarbonate (antiseptic pyolytics or WAHPSs) [40, 107, 108]. The fact is that intrapulmonary (intrarespiratory) antiseptic pyolytics developed on the basis of hydrogen peroxide have pyolytic, mucolytic, hemolytic, expectorant, bleaching and oxygen-releasing effects [40, 50, 51]. However, oxygen-releasing antiseptic pyolytics have only recently been invented, so they are still little known to specialists.

3.3. Antiseptic Pyolytics Created by Physical-chemical Repurposing of Aqueous Hydrogen Peroxide Solution as a Promising Expectorant and Anti-hypoxic Drugs

Antiseptic pyolytics were first developed at the beginning of the 21st century by physicochemical repurposing of standard cold solutions of 3-6% hydrogen peroxide, which are characterized by such physical-chemical properties as temperature around +24 - +26°C, hypotonic and acidic activity. The development of antiseptic pyolytics became possible due to the purposeful change in the physical-chemical properties of these solutions: alkalinization to pH 8.4, giving isotonic activity within 280-300 mosmol/L of water, or hypertonic activity more than 600 mosmol/L of water and heating of drug solutions to +42 - +45° C [100, 109]. Initially, such a change in the physical-chemical properties of old (known) drugs in order to create new drugs was considered a new direction in pharmacology, called physical-chemical pharmacology [100]. Nowadays, this method of searching and developing new drugs is called "physical-chemical repurposing" [110, 111]. Through this method, several warm alkaline hydrogen peroxide solutions (WAHPSs) have been developed. A significant part of drugs in this group was purposefully repurposed for emergency dissolution and removal of thick purulent masses, stimulation of aerobic metabolism in regenerating cells and the regeneration process in order to optimize the treatment of chronic wounds [109]. Since these drugs were intended mainly for the dissolution of thick purulent masses, it is possible to consider these drugs as antiseptic pyolytics [100, 109]. The fact is that warm antiseptic solution had not only pyolytic, but also antiseptic, as well as detergent, discoloration and antihypoxic action [40, 51, 100, 107-112].

Today, we can confidently report that a patent for an invention related to a WAHPS has been issued for the first time for a method of daily course cleansing of chronic wounds from purulent masses by means of irrigation of the wound surface with a solution of 3% hydrogen peroxide heated to +37°C in the interval between the removal of the old wound dressing and the application of a new dressing. In parallel with washing the wound with a warm hydrogen peroxide solution, the wound was heated with the help of a Solux lamp until the development of persistent hyperemia, but not exceeding the temperature of the wound surface +42°C for no more than 15 minutes. Then, a new wound dressing with a hypertonic solution of 2-4% sodium chloride solution heated to the temperature of +42°C was applied to the wound, and a warming element was applied over the dressing and with its help the temperature in the wound area was maintained at the level of +37°C during the whole period until the next change of the wound dressing (RU Patent No. 2187287, 20.08.2002). A few years after that a method of pleural empyema treatment was invented (RU Patent No. 2308894, 27.10.2007). The essence of this method is to introduce into the cavity heated to the temperature of +42°C alkaline solution of the surface-active drug, for example, a solution of 24% eufillin (this solution has a pH of 9.0-12.0). A year later, the method of purulent peritonitis treatment with the help of peritoneal dialysis with a carbonated solution was invented (RU Patent No. 2336833, 27.10.2008). In this invention for the first time, it was proposed to wash the purulent cavity with hypertonic sodium chloride solution heated to the temperature of +37°C and saturated with carbon dioxide or other inert gas under high pressure. In the same year, a hypergassed and hyperosmotic antiseptic agent (RU Patent No. 2331441, 20.08.2008) and a method of uterine lavage (RU Patent No. 2327471, 27.06.2008) were invented. Hypergassed and hyperosmotic antiseptic agent was an aqueous antiseptic solution consisting of 2.7-3.3% hydrogen peroxide, 0.9-10.0% sodium chloride and carbon dioxide to create an overpressure of 0.2 atm at +8°C. In turn, a solution of 0.9% sodium chloride and 3% hydrogen peroxide heated to +42 - +45°C was first proposed for uterine lavage. Then in 2009, the patent was issued for a medicinal preparation, which is a solution of hydrogen peroxide and sodium bicarbonate, intended for the liquefaction of thick and sticky pus (RU Patent No. 2360685, 10.07.2009). The invented medicinal preparation is an antiseptic in the form of aqueous antiseptic solution of 2.7-3.3% hydrogen peroxide and 5.0-10.0% sodium bicarbonate. RU patents issued from 2002 to 2009 are shown in Table **1**.

The following year, a method of preventing thrombosis of vascular catheters by periodically filling them repeatedly with a solution of 4% sodium bicarbonate was invented (RU Patent No. 2387465, 27.04.2010). A few years later, a patent was issued for a method and a medicinal preparation for the removal of a sulfur plug (RU Patent No. 2468776, 27.06.2012). A solution of 0.3-0.5% hydrogen peroxide and 1.7-2.3% sodium bicarbonate heated to +42°C was proposed as a medicinal preparation urgently dissolving the sulfur plug. At the same time, injection of WAHPS inside the sul-

fur plug was proposed as a technology for urgent dissolution of the sulfur plug. In the same year, 2012, a patent was granted for a new antiseptic intended for fistula sanitation in infected pancreonecrosis (RU Patent No. 2455010, 10.07.2012). This drug was an aqueous buffered hyperosmotic solution including 0.9% sodium chloride, 0.142% sodium hydrophosphate and 0.120% sodium dihydrophosphate. In parallel, an antiseptic pyolytic was developed for sanitation of the organ of vision and facial skin in purulent conjunctivitis, eyelid adhesion and accumulation of tear stones (RU Patent No. 2452478, 10.06.2012). This drug is an aqueous solution of 0.55-1.0% hydrogen peroxide, 1.0-1.5% sodium bicarbonate and 0.5-1.0% lidocaine hydrochloride. Analysis of these inventions convinces us that the basis of a new group of antiseptic pyolytics is a warm alkaline hydrogen peroxide solution with certain alkaline and osmotic activity. RU patents issued from 2010 to 2012 are shown in Table **1**.

Five years after that, the repurposing of hydrogen peroxide antiseptic continued in a different direction, namely toward hygienic bleaches of biological origin stains. The aim of this repurposing was to develop new preparations for urgent dissolution and whitening of plaque, food residues, dead tissues and cells of animal origin as well as dried milky plant sap on the surface of soft and hard tissues of patients' bodies, clothing and medical and household items for hygienic cleaning and whitening of teeth, dentures, washing clothes, bedding, skin and nail care. For this purpose, several WAHPSs were developed in which the concentration of hydrogen peroxide was increased and the prepared solutions were additionally saturated with oxygen gas under overpressure (RU Patent No. 2626669, 31.07.2017; RU Patent No. 2635992, 17.11.2017; RU Patent No. 2659952, 04.07.2018; RU Patent No. 2723138, 09.06.2020; RU Patent No. 2730451, 24.08.2020; RU Patent No. 2765469, 31.01.2022; RU Patent No. 2763882, 11.01.2022) (Table **1**).

Analysis of the formulation of the above hygienic stain bleaches showed that all of them are aqueous solutions containing 1.7 - 10% sodium bicarbonate (or other hydroxide or alkali), 0.01-20% hydrogen peroxide and oxygen gas or other gas under overpressure 0.2 - 4 atm at pH 7.4-14.0, osmotic activity 350-560 mosmol/L of water and local temperature +38 - +42°C.

In parallel, hydrogen peroxide was repurposed as a clot buster, blood clots and bleaches for blood stains and marks. The drugs in this group were called “bruise bleaches” [109]. It turned out that bruise bleaches had hemolytic and bleaching effects both on the surface of various objects and inside blood vessels, vascular catheters and other medical devices, as well as inside the skin and subcutaneous fatty tissue, for example, in case of bleeding. The first patents for bruise bleaches were granted in 2009. The development of such medicines began with the development of a method for the treatment of coagulated hemothorax (RU Patent No. 2368333, 27.09.2009) and a method for express removal of blood stains from clothes (RU Patent No. 2371532, 27.10.2009). In case of dissolution and removal of blood clots was offered a solution of 5% sodium bicarbonate and 1.5% hydrogen peroxide heated to +37°C, and for discoloration of blood stains on clothes was offered a solution containing hydrogen peroxide or its water-soluble source from 0.01 to 15% of the total weight of the composition of alkaline detergent at a temperature of +26 to +42°C. The following year a patent was granted for the method of elbow vein catheterization (RU Patent No. 2387465, 27.04.2010), in which a solution of 4% sodium bicarbonate was proposed to prevent thrombosis of vascular catheters and veins. In the next few years, additionally, several hygienic medicinal preparations created for the discoloration of blood-stained medical bandages, clothing and skin in the area of bruises were invented (RU Patent No. 2539380, 20.01. 2015; RU Patent No. 2589682, 10.07.2016; RU Patent No. 2586278, 10.06.2016; RU Patent No. 2573382, 20.01.2016; RU Patent No. 2582215, 20.04.2016; RU Patent No. 2600504, 20.10.2016; RU Patent No. 2631593, 25.09.2017; RU Patent No. 2631592, 25.09.2017; RU Patent No. 2639283, 20.12.2017; RU Patent No. 2639485, 21.12.2017; RU Patent No. 2641386, 17.01.2018; RU Patent No. 2647371, 15.03.2018; RU Patent No. 2653465, 08.05.2018; RU Patent No. 2679334, 07.02.2019) (Table **1**).

Analysis of the essence of new hygienic medicinal preparations of this group shows that their basis is warm aqueous solutions of hydrogen peroxide and sodium bicarbonate. As a rule, developed alkaline peroxide bleaches contain 0.01-3% hydrogen peroxide and 1.7-10% sodium bicarbonate at pH 7.4-8.5 and temperature +37-+42°C.

Additionally, hydrogen peroxide was successfully repurposed into antihypoxants between 2015 and 2017. Moreover, the first patent was granted for an alkaline isotonic saline solution of hydrogen peroxide intended for saturation of venous blood with oxygen (RU Patent No. 2538662, 10.01.2015) (Table **1**). The said drug was an aqueous solution of 0.85% sodium chloride, 0.10% sodium bicarbonate and 0.05-0.29% hydrogen peroxide. It was shown that injection of this solution into a portion of preserved donor venous blood provided urgent conversion of venous blood into arterial blood by catalase cleavage of hydrogen peroxide into water and oxygen gas and its assimilation by blood erythrocytes. A few months later in the same year, a patent was issued for a method of preserving live fish during transportation and storage (RU Patent No. 2563151, 20.09.2015) (Table **1**). In this method, it was proposed to introduce a calculated dose of 6% hydrogen peroxide solution into the water with fish instead of oxygen gas. It was shown that regular reintroduction of hydrogen peroxide solution into the water with fish replaces oxygen gas because fish absorb hydrogen peroxide, which is immediately decomposed under the action of the enzyme catalase into water and oxygen gas (Fig. **4**).

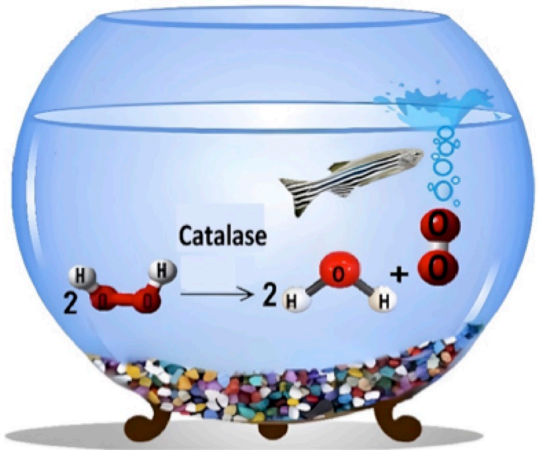


Fig. (4). Reaction of hydrogen peroxide cleavage under the influence of catalase. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

The following year, a patent was granted for a drug that was a water drink containing hydrogen peroxide and oxygen gas under high pressure. Such a drink was developed to increase the resistance of people to hypoxia (RU Patent No. 2604129, 10.12.2016) (Table **1**). The composition of such a drink included 0.3-0.5% hydrogen peroxide enriched with oxygen at an overpressure of 0.2 atm. It was shown that oxygenated hydrogen peroxide solution provides increased resistance of the organism to hypoxia in conditions of respiratory failure due to additional involvement in the gas exchange of the gastric mucosa and intragastric flow of oxygen into the blood. In the same year 2016, a patent was granted for a hydrogen peroxide drug solution for injection (RU Patent No. 2586292, 10.06.2016) (Table **1**). This medicinal solution for injection was named "Lymphatic substitute" and contained 0.88% sodium chloride, 0.06-0.1% glucose and 0.01-0.02% hydrogen peroxide, at pH 7.4, with an osmotic activity of 280 mOsmol/L water. The said antihypoxant was developed for injection into tissues during their ischemia and hypoxia in order to locally preserve their viability under oxygen deficiency. Then in 2017, patents were granted for 2 inventions (Table **1**): an energy drink (RU Patent No. 2639493, 21.12.2017) containing 0.3-0.5% hydrogen peroxide and oxygen gas under overpressure of 0.2 atm, and a drug that increases physical endurance (RU Patent No. 2634271, 24.10.2017), which is a drink containing 7% glucose, 3% hydrogen peroxide and oxygen gas before creating an overpressure of 0.2 atm. Analysis of the formulation of these new antihypoxants shows that all of them are aqueous solutions of 0.01 - 3% hydrogen peroxide, which additionally can contain oxygen gas under overpressure of 0.2 atm.

Thus, at the beginning of the 21st century, hydrogen peroxide solution was repurposed many times from antiseptics to pyolytic, hemolytic, mucolytic, bleaching and antihypoxic drugs. The peak of new hydrogen peroxide-based drug development was observed on the eve of the outbreak of a new coronavirus pandemic (Fig. **5**).

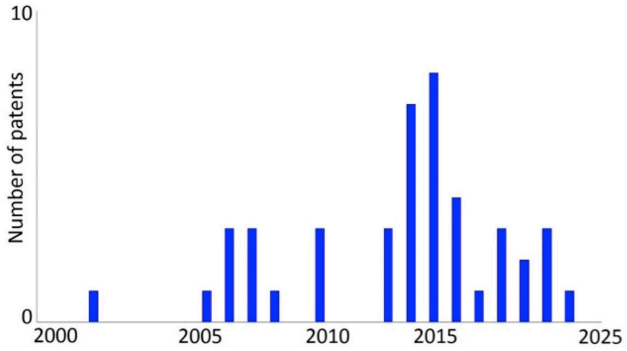


Fig. (5). Dynamics of new drug development based on hydrogen peroxide solution in the 21st century. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Consequently, initial results of successful repurposing of hydrogen peroxide into antiseptic pyolytics, bio-based stain cleaners, bruise bleaches, and enteral and injectable antihypoxants indicate the prospect of repurposing hydrogen peroxide into intrapulmonary expectorants and intrapulmonary antihypoxants.

3.4. Pharmacodynamics and Pharmacokinetics of Warm Alkaline Hydrogen Peroxide Solution in Interaction with Sputum, Mucus and Pus

It has been reported that the need for new anti-infective drugs has increased significantly in recent years, not only because of new coronavirus disease but also because of the increasing resistance of infectious agents to anti-infective drugs and the increasing number of elderly and senile patients [111, 113-115]. At the same time, the repurposing of known drugs, including antiseptics, has become a new paradigm for the search and development of new drugs [116-119]. It has been shown that about 40 WAHPSs have been developed as a result of successful physico-chemical repurposing of hydrogen peroxide. Many of them have been found to actively dissolve, decolorize, and turn into a soft oxygenated foam, pus, sputum, mucus and serous fluid of the respiratory tract, blood, blood clots, dried blood stains, bruises, lacrimal stones, sulfur plugs, meconium, keratinized epithelium, dental plaque, stains left by crushed insects and thickened dandelion milky juice [40, 50, 51, 111, 112, 117, 120-122]. This success inspired researchers to physical--chemical repurpose hydrogen peroxide into novel inhaled expectorants and intrapulmonary antihypoxants. The prospectivity of this direction was substantiated by the positive results of preliminary results of hydrogen peroxide repurposing into injectable and enteral antihypoxants [111, 122-129].

At present, the mechanism of local action of the developed alkaline hydrogen peroxide solutions is fully established [100, 117, 121]. It is very important that all WAHPSs have alkaline activity. Therefore, when interacting with thick and/or colloidal liquids containing the enzyme catalase (sputum, mucus, pus of respiratory tracts, blood, sulfur plugs, dental plaque), WAHPSs cause alkaline saponifica-

tion of protein-lipid complexes in these biological masses, which leads to their dissolution. Additionally, the local pharmacodynamics and pharmacokinetics of WAHPSs are related to the biochemical activity of the enzyme catalase, which is abundant in these biological masses. The point is that catalase decomposes hydrogen peroxide into oxygen gas and water. High intensity of oxygen formation leads to rapid formation of gas bubbles in biological masses. As a result, the biological masses begin to literally "boil" due to the cold boiling process. The cold boiling process destroys ("explodes") thick colloidal masses and turns them into soft oxygen foam of white color. At the same time, oxygen has deodorizing, antiseptic, decolorizing and antihypoxic effects [40, 51, 111]. In addition, it is reported that small doses of oxygen participate in the conversion of carbohemoglobin into oxyhemoglobin, and large doses participate in the oxidative decolorization of hemoglobin and its colored metabolites [112, 126]. The decolourization of hemoglobin is accompanied by the release of heat [127, 128].

However, until 2020, WAHPSs were not proposed as intrapulmonary expectorants and antihypoxants for airway clearance and hypoxemia relief in respiratory obstruction caused by obstructive purulent bronchitis in COVID-19. The fact is that the cause of respiratory obstruction was considered to be edema of the mucous membranes of the airways, as in asthma, but not the accumulation of sputum, mucus and pus in the airways. However, in recent years, there have been reports that COVID-19-induced acute respiratory infections are often triggered by associated bacteria that can cause not only acute lung injury but also accumulation of mucus and pus in the respiratory tract [86, 87, 129]. It has been shown that respiratory obstruction can be caused by airway accumulation of mucus, sputum, pus, serous fluid, fibrous fluid, plasma, blood, and some other types of colloidal bodily fluids in the airways, especially in patients with bacterial or fungal superinfection, tuberculosis, pulmonary strongyloidiasis, Legionnaires' disease, or chest trauma [40]. This may explain the suggestion that when airways are obstructed by sputum, mucus, pus, and/or blood, inhalation of WAHPSs may improve lung ventilation, airway patency for inhaled corticosteroids and oxygen, and increase oxygen absorption into the blood during a severe asthma attack [27, 50, 107].

Consequently, inhalation of WAHPSs has the potential to urgently recanalize the airways and increase blood oxygenation through the lungs when the airways are obstructed by sputum, mucus, pus, and blood [27, 40, 50, 51, 108]. However, the standard of care for choking due to severe asthma attacks or respiratory obstruction in COVID-19 does not include WAHPSs in the role of intrapulmonary antiseptics, mucolytics, pyolytics, expectorants, and antihypoxants [40, 129-131].

3.5. Inhalation of Aerosols and Intrapulmonary Injections of Warm Alkaline Hydrogen Peroxide Solutions: Pharmacodynamics and Pharmacokinetics

WAHPSs were first proposed for the treatment of obstructive purulent bronchitis as inhaled expectorants in 2020. For this purpose, it was recommended to use WAHPSs in the form of an aerosol with microparticle sizes in the range of 0.5-2 μm for inhalation at +41- +55°C (RU Patent No. 2735502, 03.11.2020) (Table **1**). In this case, the WAHPSs aerosol for inhalation was reported to contain 0.3-0.5% hydrogen peroxide and 1.2% sodium bicarbonate. It was shown that at the prehospital stage of treatment of a severe asthma attack combined with purulent obstructive bronchitis, inhalation of the developed WAHPS aerosol provides urgent expectorant and antihypoxic effect with a single application [40, 50, 51, 108]. Shortly thereafter, another WAHPS aerosol for inhalation was developed to optimize artificial lung ventilation in case of airway obstruction by thick sputum, mucus and pus in the terminal stage of nonspecific bilateral pneumonia in COVID-19. In this case, WAHPS also contains 0.3-0.5% hydrogen peroxide, but unlike the previous WAHPS it contains not 1.2% but 2-10% sodium bicarbonate, which increases its alkaline buffering activity and gives it a hypertonic activity (patent RU Nº 2742505, 08.02.2021) (Table **1**). In addition, this aerosol was recommended for inhalation at the temperature of +37 - +55°C. It was co-reported that the developed inhaled WAHPS improves airway patency for respiratory gases, increases blood oxygenation through the lungs during artificial ventilation and eliminates hypoxemia in resuscitation patients [50, 51, 108].

After that, it was decided to increase the resuscitation efficiency of WAHPSs in case of airway obstruction by thick sputum, mucus and pus by using WAHPSs by intrapulmonary injections. The results of the first experiments confirmed the correctness of this assumption [40, 50, 51, 129, 132]. The studies were carried out in laboratory and experimental conditions using the original model of acute respiratory obstruction in live rabbits and in isolated rabbit lungs. To model respiratory obstruction, the airways were filled through the trachea with artificial sputum containing the enzyme catalase (RU Patent No. 2748999, 02.06.2021) (Table **1**) [27]. Although catalase is found in many animal tissues [133, 134], it is more convenient and safe to use animal blood to introduce this enzyme into artificial sputum. Under conditions of model respiratory obstruction, drug screening was carried out under the control of lung airiness and/or dynamics of blood oxygen saturation indices using a pulse oximeter placed on the rabbit ear. Experimental results showed that a single intrapulmonary injection of WAHPS leads to an immediate conversion of thick artificial to white oxygen foam inside the airways, to an increase in lung airiness, to a very rapid release of white foam from the trachea and a very rapid increase in blood oxygenation (RU application No. 2021102618, 04.08.2022) (Table **1**). It was reported that under conditions of acute hypoxemia in mongrel rabbits at the value of blood oxygenation index 45 - 50%, a single intrapulmonary injection of 2 ml of WAHPS provided immediate expectoration of artificial sputum in the form of white foam, restoration of natural respiration and increase in blood oxygenation. Moreover, the value of the blood oxygenation

index reached 90% not later than 12 seconds after intrapulmonary injection of WAHPS [107, 108, 126-129].

Finally, in 2023, a patent for the invention "Warm alkaline hydrogen peroxide solution for intrapulmonary injection" (RU Patent No. 2807851, 21.11.2023) was obtained for the first time (Table **1**). It is reported that the essence of this invention is that WAHPS has a volume of 30 ml, is heated to a temperature of +42°C, includes water for injection, 4.5% hydrogen peroxide, 1.8% sodium bicarbonate and oxygen gas to create an overpressure of 0.2 atm with an osmotic activity of 280 - 300 mosmol/L of water and alkaline activity in the range of pH 8.4 - 8.5. It was shown that in this case, intrapulmonary injection of 0.2 - 0.5 ml of oxygenated WAHPS caused immediate (at the end of the needle) discoloration of lung tissue around the injection site and white foam release from the trachea. Moreover, the foam was released from the trachea of the isolated lung with hissing and splashing drops. Immediately after completion of intrapulmonary injections of 0.2 ml of oxygenated WAHPS into each lung lobe, all visible tissue of both lungs changed color from light cherry to light pink. In 10 seconds after the onset of the foaming process, the foam was suctioned from the trachea and simulated artificial ventilation with air was started. The lungs were easily and completely inflated when air was pumped into them and evenly collapsed when no air was pumped into the lungs through the trachea.

4. DISCUSSION

The COVID-19 virus emerged in China in late 2019 and quickly spread around the world, infecting more than half a billion people and causing the death of one-hundredth of them. To date, it has been possible to create a preventive vaccine that is effective in more than 95% of cases [76, 135-137]. However, despite the availability of an effective vaccine against the new coronavirus infection and ongoing mass vaccination of the population, protection against the new infection may be negated by the emergence of new SARS-CoV-2 variants [138-140]. Acute respiratory distress syndrome remains a severe complication of final-stage COVID-19 with significant mortality caused by hypoxemia, most commonly due to pneumonia and loss of lung airiness [141-143]. Treatment of ARDS remains largely supportive and includes nasal oxygenation, noninvasive respiratory support, and invasive artificial ventilation [143, 144]. Therefore, ARDS and COVID-19 have a close relationship and both have attained "Bermuda Triangle" status in the field of drug development, as no effective drugs have been found so far [145-147]. Nevertheless, the search for new drugs continues. However, there is no universally recognized promising direction search for new drugs for the effective management of ARDS. In recent years there have been reports that one promising avenue for finding effective drugs may be the physicochemical repurposing of the antiseptic hydrogen peroxide into inhaled and intrapulmonary oxygen-releasing mucolytic and pyolytics [27, 40, 50, 51, 117, 120, 121].

The likelihood of developing effective inhaled and intrapulmonary antihypoxants by physical-chemical conversion of hydrogen peroxide to oxygen-releasing pyolytics is due to the following circumstances. It has been reported that hypoxia and high mortality in elderly patients with COVID-19 may be exacerbated by the presence of excessive thick sputum, mucus and pus in the bronchi and serous fluid in the alveoli [86, 87, 146-149]. It has been shown that sputum, mucus, serous fluid, purulent masses, and even blood contain the enzyme catalase, which very rapidly breaks down hydrogen peroxide into water and oxygen gas [150]. However, developers of new drugs for a long time paid little attention to this potential factor of local interaction. Therefore, inhalation and intrapulmonary pyolytic and mucolytic oxygen-releasing antihypoxants developed by repurposing hydrogen peroxide have only recently been discovered [108, 129, 132]. In particular, up to the present time, hydrogen peroxide solutions are classified as antiseptics and are used for the sanitation of acute and chronic wounds [109, 151]. In this regard, the clinical use of hydrogen peroxide solutions is limited only to the elimination of microbial contamination and only sometimes to the achievement of hemostasis [152].

According to the established medical practice, 3-6% hydrogen peroxide solution has been traditionally used for medical purposes for more than 100 years, which always had acidic activity [153]. For long-term storage of the hydrogen peroxide solution, it is recommended to add a stabilizer to this solution (US Patent No 3383174, May 14, 1968), namely a small amount of pyrophosphoric acid, or to stabilize the acidity of the solution in another way in the pH range of 1.0 to 7.0 (US Patent No 6327963, January 14, 1936). Nevertheless, a better understanding of the ability of hydrogen peroxide solutions to dissolve thick sputum, mucus, serous fluid, pus, and blood clots, as well as to expectorate these thick colloidal masses from the respiratory tract and to generate oxygen gas in the respiratory tract with their help may increase the potential for combating hypoxemia during natural and artificial ventilation [127, 132]. Moreover, better and faster disclosure of the potential ability of inhaled and intrapulmonary hydrogen peroxide to exert pyolytic, mucolytic, expectorant and oxygenating effects in the lungs during respiratory obstruction can be achieved by taking into account such physical-chemical properties of hydrogen peroxide solutions as alkaline, hyperthermic, osmotic and oxygen releasing activity [111, 117, 154].

An analysis of the literature and patents for inventions has shown that in the last 20 years, the physical-chemical repurposing of hydrogen peroxide from antiseptics to antiseptic pyolytic, bruise bleaching, oxygen alkaline dental's cleaners, expectorant, pyolytic, mucolytic, haemolytic, oxygen-releasing, and decolorizing drugs has been successfully carried out [121]. To date, more than 40 new drugs have been developed from hydrogen peroxide, most of which are warm alkaline hydrogen peroxide solutions [126]. The dynamics of the development and patenting of new drugs based on alkaline hydrogen peroxide solutions in the 20th and 21st centuries are presented in Table **1**.

Table 1. List of patents for invented new medicines based on alkaline hydrogen peroxide solution in the XX and XXI century.

S. No.	Purpose	Patent No. and Data Publication
20th Century (from 1936 to 1999)		
1	Preservation of hydrogen peroxide due to the acidity of the solution	US Patent No. 6327963, 14.01.1936
2	Preservation of hydrogen peroxide due to the acidity of the solution	US Patent No. 3383174, 14.05.1968
21st Century (Jan. 2000 - Dec. 2004)		
3	The splitting of hydrogen peroxide in an alkaline environment by catalase of biological fluids into water and oxygen, which turns the fluids into foam	RU Patent No. 2187287, 20.08.2002
21st Century (Jan. 2005 - Dec. 2009)		
4	Dissolution of thick pus by alkalinity and hyperthermia	RU Patent No. 2308894, 27.10.2007
5	The splitting of hydrogen peroxide in an alkaline environment by catalase of biological fluids into water and oxygen, which turns the fluids into foam	RU Patent No. 2327471, 27.06.2008
6	-"-	RU Patent No. 2331441, 20.08.2008
7	-"-	RU Patent No. 2336833, 27.10.2008
8	-"-	RU Patent No. 2360685, 10.07.2009
9	-"-	RU Patent No. 2368333, 27.09.2009
10	-"-	RU Patent No. 2371532, 27.10.2009
21st Century (Jan. 2010 - Dec. 2014)		
11	Hemolytic action due to alkalinity	RU Patent No. 2387465, 27.04.2010
12	The splitting of hydrogen peroxide in an alkaline environment by catalase of biological fluids into water and oxygen, which turns the fluids into foam	RU Patent No. 2452478, 10.06.2012
13	-"-	RU Patent No. 2468776, 27.06.2012
14	-"-	RU Patent No. 2455010, 10.07.2012
21st Century (Jan. 2015 - Dec. 2019)		
15	The splitting of hydrogen peroxide in an alkaline environment by catalase of biological fluids into water and oxygen, which turns the fluids into foam	RU Patent No. 2538662, 10.01.2015
16	-"-	RU Patent No. 2539380, 20.01.2015
17	-"-	RU Patent No. 2563151, 20.09.2015
18	-"-	RU Patent No. 2573382, 20.01.2016
19	-"-	RU Patent No. 2582215, 20.04.2016
20	-"-	RU Patent No. 2586278, 10.06.2016
21	-"-	RU Patent No. 2586292, 10.06.2016
22	-"-	RU Patent No. 2589682, 10.07.2016
23	-"-	RU Patent No. 2600504, 20.10.2016
24	-"-	RU Patent No. 2604129, 10.12.2016
25	-"-	RU Patent No. 2626669, 31.07.2017
26	-"-	RU Patent No. 2631592, 25.09.2017
27	-"-	RU Patent No. 2631593, 25.09.2017
28	-"-	RU Patent No. 2634271, 24.10.2017
29	-"-	RU Patent No. 2635992, 17.11.2017
30	-"-	RU Patent No. 2639283, 20.12.2017
31	-"-	RU Patent No. 2639485, 21.12.2017
32	-"-	RU Patent No. 2639493, 21.12.2017
33	-"-	RU Patent No. 2641386, 17.01.2018
34	-"-	RU Patent No. 2647371, 15.03.2018
35	-"-	RU Patent No. 2653465, 08.05.2018
36	-"-	RU Patent No. 2659952, 04.07.2018
37	-"-	RU Patent No. 2679334, 07.02.2019
21st Century (Jan. 2015 - Dec. 2019)		
38	The splitting of hydrogen peroxide in an alkaline environment by catalase of biological fluids into water and oxygen, which turns the fluids into foam	RU Patent No. 2723138, 09.06.2020
39	-"-	RU Patent No. 2730451, 24.08.2020

S. No.	Purpose	Patent No. and Data Publication
40	-“-	RU Patent No. 2735502, 03.11.2020
41	-“-	RU Patent No. 2742505, 08.02.2021
42	-“-	RU Patent No. 2748999, 02.06.2021
43	-“-	RU Patent No. 2763882, 11.01.2022
44	-“-	RU Patent No. 2765469, 31.01.2022
45	-“-	RU Application No. 2021102618, 04.08.2022
46	-“-	RU Patent No. 2807851, 21.11.2023

Patents:

1. Stabilization of hydrogen peroxide. US Patent No. 6327963.
2. Stabilization of hydrogen peroxide. US Patent No. 3383174.
3. Method for treating long-term non-healing wounds. RU Patent No. 2187287.
4. Method for treating pleural empyema cases. RU Patent No. 2308894.
5. Uterine lavage technique. RU Patent No. 2327471.
6. Hyper-gassed and hyper-osmotic antiseptic mixture. RU Patent No. 2331441.
7. Method for peritoneal dialysis using gasified solution. RU Patent No. 2336833.
8. Means for liquidating thick and sticky pus. RU Patent No. 2360685.
9. Methods of diagnostics and treatment of clotted hemothorax by A.Y. Malchikov. RU Patent No. 2368333.
10. Method of express cleaning of blood stains off clothes. RU Patent No. 2371532.
11. Method for ulnar vein catheterisation and multiple-dose intravenous drugintroduction. RU Patent No. 2387465.
12. Multipurpose solution for epibulbar instillations. RU Patent No. 2452478.
13. Method and means for removing a sulfur plug. RU Patent No. 2468776.
14. Agent for fistula sanitation in infected pancrenecrosis. RU patent No. 2455010.
15. E. M. Soikher's hyperoxygenated agent for venous oxygen saturation. RU Patent No. 2538662.
16. Bruise bleacher. RU Patent No. 2539380.
17. Method of maintenance of live fish during transportation and storage. RU Patent No. 2563151.
18. Agent for intradermal bruise whitening. RU Patent No. 2573382.
19. Method for skin discoloration in bruising area. RU Patent No. 2582215.
20. Method for skin discoloration in bruising area. RU Patent No. 2586278.
21. Lympho-subsitute for local maintaining viability of organs and tissues in hypoxia and ischemia. RU Patent No. 2586292.
22. Bleaching agent RU Patent No. 2589682.
23. Method of removing paint from skin. RU Patent No. 2600504.
24. Agent for increasing resistance to hypoxia. RU Patent No. 2604129.
25. Frictional toothpaste. RU Patent No. 2626669.
26. Method for whitening of sore under nail. RU Patent No. 2631592.
27. Method for emergency bleaching and blood crust removal from skin in place.
of squeezed out acne. RU Patent No. 2631593.
28. Means for physical endurance increase. RU Patent No. 2634271.
29. Aerated mouthwash. RU Patent No. 2635992.
30. Method for whitening of bruise under eye. RU Patent No. 2639283.
31. Means for intravital skin whitening near blue eyes. RU Patent No. 2639485.
32. Energy drink RU Patent No. 2639493.
33. Method for blue nail treatment. RU Patent No. 2641386.
34. Decolorant of blood. RU Patent No. 2647371.
35. Bleaching opener of dried blood for wrapping bandages adhered to a wound. RU Patent No. 2653465.
36. Bleaching cleanser of dentures. RU Patent No. 2659952.
37. Method of emergency bleaching of skin hematoma under eye. RU Patent No. 2679334.
38. Method of using plaque removal solution with irrigation agent. RU Patent No. 2723138.
39. Peeling agent for foot hyperkeratosis. RU Patent No. 2730451.
40. Aerosol for inhalation in obstructive bronchitis. RU Patent No. 2735502.
41. Aerosol for invasive mechanical ventilation in COVID-19. RU Patent No. 2742505.
42. Artificial sputum for modeling respiratory obstruction in COVID-19. RU Patent No. 2748999.
43. Glass washing liquid. RU Patent No. 2763882.
44. Dandelion milky juice stains bleaching agent. RU Patent No. 2765469.
45. Method of pulmonary oxygenation in COVID-19. RU Application No. 2021102618.
46. Warm alkaline hydrogen peroxide solution for intrapulmonary injection. RU Patent No. 2807851.

It was found that the effectiveness of hydrogen peroxide solution on pus, mucus, sputum and blood clots depends most of all on the concentration of hydrogen peroxide, alkaline activity and heating of the solution. It has been reported that increasing the temperature of hydrogen peroxide solution from +24 to +55°C and the pH value from 7.0 to 8.5 increases its pyolytic, mucolytic, hemolytic, bleaching and oxygen-releasing activity [118]. It has been shown that the indicated level of hyperthermia and alkalinity is achieved by simply physically heating the solution and administering sodium bicarbonate. It was reported that increasing the temperature of the interacting media accelerates the process of alkaline saponification of proteins and protein-lipid complexes that form the basis of colloidal biological masses, accelerates and enhances the process of enzymatic decomposition of hydrogen peroxide into water and oxygen gas, occurring under the action of the enzyme catalase, which is always present in most biological masses. The molecular oxygen released forms gas bubbles, which simulate the process of cold boiling and due to this “explodes” biological masses, turning them into fluffy white foam. The point is that oxygen in an alkaline environment oxidizes biological pigments, including hemoglobin and its metabolites of different colors, and discolors them [100, 126].

Analysis of the essence of WAHPSs showed that all of them contain hydrogen peroxide and sodium bicarbonate in previously unknown concentrations and combinations. The most remarkable is that the created preparations can be divided into 3 groups depending on the content of hydrogen peroxide in them, the concentration values of which are in the

range of 0.03 - 20% [40]. It was reported that solutions with very low values of hydrogen peroxide concentration are intended for injection into living tissues (venous blood, skin, myocardium, brain, *etc*.) in order to increase their oxygen content in hypoxia or ischemia without the formation of gaseous oxygen bubbles, embolization of tissues and blood vessels. Solutions with medium concentration values of hydrogen peroxide are intended for injections and/or irrigation of dense biological tissues that have "outlived their age" (sulfur plugs, pus, plaque, *etc*.) in order to dissolve them and/or turn them into fluffy oxygen foam without strong "ruptures" at cold boiling and without destroying the structure of surrounding living tissues. Solutions with the highest concentration values of hydrogen peroxide are designed for local interaction with solid non-living biological tissues (keratinized layer of epidermis, dried spots of crushed insects, dried spots of plant milky juice, *etc*.) in order to urgently destroy their structure, complete dissolution, bleaching and removal.

The conducted multilateral studies showed the uniqueness of the pharmacological effects of WAHPSs. Local application of WAHPSs has shown their promise for the development of inhaled and intrapulmonary pyolytic and mucolytic antihypoxants. The finding that the local interaction of WAHPSs with thick sputum, mucus, pus, meconium, and/or blood clots results in the fastest possible conversion to a lush oxygen-containing foam when WAHPSs are enriched with oxygen gas under overpressure can be recognized as a real discovery [155, 156].

In 2023, the first reports emerged that WAHPSs can be claimed to be inhaled and intrapulmonary injectable expectorants, mucolytics, pyolytics, hemolytic and oxygen-producing antihypoxants suitable for urgent oxygen gas filling of the airways in the presence of sputum, mucus, pus, blood, serous fluid and other colloidal fluids containing the enzyme catalase [108, 129]. These results allowed to develop a new original drug - warm alkaline hydrogen peroxide solution for intrapulmonary injections (RU Patent No. 2807851, 21.11.2023). Distinctive feature of the mentioned solution for intrapulmonary injections is that it is the first ever injectable drug solution, which is enriched with oxygen gas due to increased pressure (in this case contains oxygen gas under overpressure of 0.2 atm). It has been shown that in a model airway obstruction in isolated rabbit lungs with artificial sputum, intrapulmonary injection of OWAHPS caused immediate conversion of sputum into oxygenated foam, which was released from the trachea to the outside with hissing and splashing droplets. It was reported that 10 seconds after intrapulmonary injection of OWAHPS, the lungs of rabbits easily and completely inflated when air was pressurized into them and uniformly collapsed when no air was supplied to the lungs through the trachea. This high rate of development of the above pharmacologic effects of OWAHPS when injected intrapulmonary is excellent for providing non-emergency medical care for the threat of hypoxic brain cell damage to patients with ARDS in the final stage of COVID-19 [11, 40, 50].

It was reported that the first intrapulmonary injections of WAHPS were performed in experimental models of ARDS and hypoxemia in live mongrel rabbits (*in vivo*) and total airway obstruction in isolated rabbit lungs (*in vitro*) in 2021 [129]. For this purpose, the airways were filled with warm artificial sputum containing the enzyme catalase [27]. It was shown that intrapulmonary injection of WAHPS provided immediate conversion of artificial sputum into oxygen foam inside the airways. It was noted that the appearance of oxygen foam promoted its removal to the outside through the trachea and increased the level of oxygen in the airways and blood. Moreover, under conditions of hypoxemia, the value of blood oxygenation in mongrel rabbits normalized not later than 12 seconds after intrapulmonary injection of WAHPS [129]. Consequently, intrapulmonary injection of OWAHPS in experimental ARDS and hypoxemia immediately increases respiratory and blood oxygen levels.

The results of experimental studies prove that inhaled and injected WAHPSs and OWAHPSs cardinally differ from all known drugs in the spectrum of pharmacological effects: Inhalation of WAHPSs and especially intrapulmonary injections of OWAHPSs provide immediate conversion of sputum, mucus, serous fluid, pus, meconium and blood into oxygen foam, which immediately increases the oxygen content in the lumen of the bronchi and alveoli, increases oxygenation of blood through the lungs and eliminates severe hypoxemia. Therefore, there is every reason to assume that a promising direction for the search and development of new drugs for use in intensive care pulmonology has been found. However, there is still a lot of research to be done in the future to understand all aspects of local application of inhaled and intrapulmonary injected WAHPSs and OWAHPSs not only in experimental but also in clinical conditions.

Given the large number of WAHPSs developed from hydrogen peroxide by its physical-chemical reprofiling and the wide range of pharmacological effects induced by WAHPSs in local interaction with biological masses containing the enzyme catalase, this approach can be seriously considered for further development of new pyolytics, mucolytics, hemolytics, expectorants, bleachers and antihypoxants, with the potential to achieve excellent results. It is important to note that the mechanism of action of WAHPSs differs significantly from other drugs in that WAHPSs are intended for local application only and their local action is due to nonspecific physical-chemical factors of local interaction. Nonspecific local action of WAHPSs is provided by the following factors of local interaction: local temperature within +37 - +55°C, local alkalinity at pH 8.4- 8.5 and the presence of catalase enzyme in the interacting colloidal liquids.

Although warm alkaline hydrogen peroxide solutions have some advantages in the treatment of COVID-19, we have much more research to do in the future to ensure that WAHPS find the "right" place in the treatment regimen of patients as inhaled and intrapulmonary expectorants, pyolytic, mucolytic, antiseptic, deodorizing, and oxygen-releasing antihypoxants. This kind of research has only recently begun. The first results of hydrogen peroxide application prove its safety and are encouraging [157-161]. Multiple sclerosis

in particular seems to be rather unbalanced in favor of the efficacy of this approach. Therefore, comprehensive large-scale studies are needed to draw the right conclusions.

CONCLUSION

As described in the studies presented in this article, WAHPSs are increasingly being studied as promising pyolytic, mucolytic, hemolytic, expectorant, bleaching, and oxygen-releasing antihypoxants. Local interaction of WAHPSs with sputum, mucus, serous fluid, pus, blood, meconium and other colloidal and dense tissues containing the enzyme catalase provides very rapid dissolution and transformation into fluffy oxygen-containing foam of white color. It has been established that the local action of WAHPSs is provided by the following factors of local interaction: local hyperthermia within the limits of +37 - +55°C, local alkalinity at pH 8.4-8.5 and the presence of catalase enzyme in mutually acting media. It was found that WAHPSs dissolve biological masses due to the alkaline saponification of protein-lipid complexes. Additionally, the enzyme catalase contained in biological masses decomposes hydrogen peroxide into oxygen gas and water. In turn, the high intensity of oxygen formation leads to the rapid formation of gas bubbles and the cold boiling process in the biological masses. The process of cold boiling destroys ("explodes") thick colloidal masses and turns them into soft oxygen foam of white color. The oxygen has an antihypoxic, deodorizing, antiseptic, discoloring and warming effect.

Several inhalation and injection WAHPSs have been developed to date. In particular, a WAHPS for intrapulmonary injection has been invented which is enriched with oxygen gas due to overpressure. It has been shown that in a model airway obstruction in isolated rabbit lungs with artificial sputum, intrapulmonary injection of oxygenated warm alkaline hydrogen peroxide solution (OWAHPS) caused immediate conversion of sputum into oxygenated foam, which was released from the trachea to the outside with hissing and splashing droplets. It was reported that 10 seconds after intrapulmonary injection of OWAHPS, the lungs of rabbits were easily and completely inflated when air was forced into them and collapsed uniformly when no air was supplied to the lungs through the trachea. It has also been reported that intrapulmonary injection of WAHPS for up to 12 seconds converted artificial sputum into oxygen foam inside the airways, expelled it outward through the trachea and filled the airways with oxygen and increased blood oxygenation to normal values.

Studies conducted *in vitro* and animal models already show the great therapeutic potential of WAHPSs and OWAHPSs. Overall, despite some limited initial experimental studies, it can be assumed that WAHPSs and OWAHPSs have great appeal for the development of new drugs in the future. There is every reason to hope that inhalation and intrapulmonary injection of these drugs can significantly optimize the treatment of suffocation and hypoxemia caused by airway obstruction by thick sputum, mucus, pus, serous fluid, blood, and/or meconium. The fact is that intrapulmonary OWAHPSs provide a very high rate of development of the "right" pharmacological effects, which is excellent for emergency medical care in the threat of hypoxic brain cell damage in patients with respiratory obstruction in the final stage of COVID-19. We can only hope that in the near future, researchers will continue experimental and clinical studies, the results of which will allow us to improve the drugs and technologies of their medical use to safely transfer them from the table to the bedside of patients to reduce mortality from suffocation and hypoxemia in COVUD-19.

AUTHOR CONTRIBUTIONS

AU, NU and PS provided the conceptualization, the methodology was adopted by AR, ASh, AO and VN, software was developed by NM, validation was performed by VN and NK, formal analysis was conducted by AO, YuS and SO, AR, AU, PS and SO investigated the study, the resources were provided by AR and NK, data were curated by AU, writing—original draft preparation was done by AU, NU, ASh, VN, NM and YuS, writing-review and editing was performed by AU, AO, SO and NU and AU and PS supervised the study. All authors contributed to drafting the first manuscript, and read, and approved the final manuscript.

LIST OF ABBREVIATIONS

ARDS	=	Acute Respiratory Distress Syndrome
COVID-19	=	Coronavirus 2019
SARS	=	Severe Acute Respiratory Syndrome
WAHPSs	=	Warm Alkaline Hydrogen Peroxide Solutions

CONSENT FOR PUBLICATION

Not applicable.

STANDARD FOR REPORTING

PRISMA guidelines were followed.

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CONFLICT OF INTEREST

The authors declare no conflict of interest financial or otherwise.

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SUPPLEMENTARY MATERIAL

PRISMA checklist is available as supplementary material on the publisher's website along with the published article.

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