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Hydrogen Peroxide: Potential for Repurposing into an Oxygen-Producing Antihypoxant by Generating Oxygen Gas

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Abstract: It is reported that oxygen gas remains the number one drug of choice in ambulances and hospital intensive care units during medical emergencies to prevent hypoxic brain cell damage in hypoxemia. Generally, oxygen is used universally for this purpose during the emergency medical care phase with mechanical lung ventilation. However, in cases of airway obstruction by thick sputum, mucus, pus, and/or blood, such as in ARDS in elderly patients with COVID-19, inhaled breathing gases and oxygen gas have great difficulty reaching the alveoli, so they are poorly absorbed into the blood, poorly reduce hypoxemia and lose their ability to prevent death from hypoxic brain cell damage. It is shown that hydrogen peroxide can be used as an alternative to oxygen gas since oxygen can be its metabolite. Thirty-nine inventions based on hydrogen peroxide solutions as oxygen gas producers and as new antihypoxants, mucolytics, and pyolytics, intended for topical use and having great prospects to take a leading place among drugs intended for inhalation and intrapulmonary injection are given. Local intrapulmonary, endotracheal, and endobronchial pharmacodynamics and pharmacokinetics of hydrogen peroxide solutions are described, which are inseparable from interaction with the enzyme catalase contained in sputum, mucus, serous fluids, purulent masses, and blood.

Keywords: gas oxygen; hydrogen peroxide; catalase; ARDS; hypoxemia; antihypoxants; pyolytics; mucolytic.
List of abbreviations: ALV = artificial lung ventilation; ARDS = acute respiratory distress syndrome; COVID-19 = Coronavirus 2019; WAHPSs = warm alkaline hydrogen peroxide solutions.

1. Introduction

The pandemic caused by a new coronavirus infection, supplemented more recently by a large number of transmissible variants (Delta and Omicron), continues to claim millions of lives around the globe despite humanity's best efforts to combat COVID-19 [1]. In severe cases, the disease manifests as nonspecific pneumonia, complicated in the final stage by acute respiratory distress syndrome (ARDS), leading to hypoxemia and death [2]. Hypoxic brain cell damage is the biological cause of death in all patients [3,4]. It has been reported that children and adults die from COVID-19 less often than the elderly [5]. People living in nursing homes are particularly vulnerable [6-8]. It was shown that the dynamics of sputum accumulation in the respiratory organs of those who died from a new coronavirus disease had been previously not investigated [9-11]. Under these circumstances, the first report in 2020 was that one of the

causes of suffocation, hypoxemia, and death in COVID-19 may be the excessive accumulation of thick sputum, mucus, and pus in the airways [12-17]. Simultaneously, there was evidence that urgent blood oxygenation through the lungs could be achieved with a single injection of hydrogen peroxide solution into the airways. Inhalation or intrapulmonary injection of an alkaline hydrogen peroxide solution for airway obstruction by sputum, pus, mucus, and/or blood has been shown to provide immediate conversion to oxygen foam and absorption of oxygen into the blood through the lungs [12-19]. Since 2023, the significance of sputum, mucus, and pus accumulation in the airways as a risk factor for death in COVID-19 in the elderly has been confirmed by other researchers [20-23].

In this article, we intend to review alkaline hydrogen peroxide solutions as a promising group of drugs for intrapulmonary oxygen production, the resuscitative potential of which, in the case of complete obstruction of the respiratory tract, is revealed due to the rapid splitting of hydrogen peroxide (H_2O_2) into water and gaseous oxygen, the alkaline dissolution of thick sputum, mucus, pus and blood, while simultaneously converting them into oxygen foam inside the respiratory tract and increasing blood oxygenation through the lungs.

Information contained in inventions and scientific articles was used. The following databases were searched for information in the scientific literature: PubMed, Medline, Scopus, Web of Science, Google Scholar, Index Copernicus, Crossref, Questel-Orbit, Science Direct, Yandex, and E-library. In addition, the information in the "References" section of the selected scientific articles was studied. 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, analogs and prototypes indicated in the selected inventions were studied. Search queries used in various combinations included “COVID-19”, “coronavirus”, “SARS-CoV-2”, "respiratory obstruction", “suffocation”, “asphyxia”, "hypoxia", “hypoxemia”, “brain cells”, “hypoxic injury”, “damage”, “resistence”, “stability”, “survival rate”, “viability”, “hydrogen peroxide”, “catalase”, “water”, “oxygen”, “oxygen therapy”, “air”, “antihypoxants”, “inflammation", “airways”, “pneumonia”, “bronchitis“, “lungs”, “alveoli”, "mucous membrane", “ARDS”, “sputum”, “mucus”, “pus”, "serous fluid", "blood", "saturation", "aerosol", "inhalation", “intrapulmonary”, "bronchodilators", "mucolytics", "pyolytics", “drugs”, "corticosteroids", "antihistamines", "sodium bicarbonate", "solution", "antiseptics", "disinfectants", "expectorants", “chemotherapy”, “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.

In the review, we relied on information about drugs, devices, and medical technologies suitable for the immediate conversion of serous fluid, thick sputum, mucus, pus, meconium, and/or blood in the respiratory tract into oxygen foam and increasing blood oxygen saturation through the lungs. The following criteria were used to exclude a piece of information from the review: unsuitability for administration into edematous lung tissue and/or airways when obstructed for immediate oxygenation of thick sputum, mucus, serous fluid, pus, lymph, blood, and/or meconium therein, and lack of absolute novelty worldwide and/or patent pending. At the same time, we relied more on the content of inventions rather than on the content of scientific articles. The fact is that it is an invention and not a scientific article, the generally accepted criterion of absolute novelty in the world. At the same time, inventions are developed before scientific articles are written.

Since the possibility of developing new oxygen-producing antihypoxants by physical-chemical repurposing of hydrogen peroxide has been actively explored in recent years, this review article aimed to analyze the recent advances in this field. It was supposed to reveal the medical potential of new oxygen-producing antihypoxants based on the catalase generation of oxygen gas from warm alkaline hydrogen peroxide solutions when applied locally in the respiratory organ in cases of acute asphyxia caused by airway obstruction by thick sputum, serous fluid, pus and/or blood.

2. Mechanism of Oxygen-Producing Antihypoxic Effect of Warm Alkaline Hydrogen Peroxide Solutions During their Endotracheal, Endobronchial, and Intrapulmonary Injection in Case of Airway Obstruction by Sputum, Pus, Mucus, and/or Blood

The study of H_2O_2 as an oxygen-producing antihypoxant that replaces gaseous oxygen and prevents hypoxic damage to brain cells in hypoxia began in December 2013. At that time, the first patent application was registered for a method of transporting and storing live fish in water with a solution of 6% hydrogen peroxide added to the water to produce oxygen from it and keep the fish alive under hypoxic conditions [24,25]. Today, it became clear that other researchers conducted similar studies for the first time only 10 years later [26]. However, in these studies on fish, the molecular mechanisms of the antihypoxic effect of H_2O_2 have not been clarified. Meanwhile, by mid-2024, 14 inventions have been developed in which the original hydrogen peroxide solutions, which play the role of oxygen-producing antihypoxants, have been used to prevent hypoxic-ischemic cellular damage in living tissues under oxygen-deficient conditions (Table 1).

Table 1. Inventions in which, for the prevention of hypoxic-ischemic damage to cells of living tissues with a lack of oxygen, repurposed hydrogen peroxide was proposed as an oxygen-producing antihypoxant.

Number in order	Authors, title of invention, number of patent or application, date of the patent publication or registration of the application
	Hydrogen peroxide solutions for injection into a portion of water or venous blood
1	Urakov AL, Urakova NA, Agarval RK, Reshetnikov AP, Chernova LV. Method of maintenance of live fish during transportation and storage. Patent RU2563151C1, 20.09.2015.
2	Urakov AL, Urakova NA, Reshetnikov AP, Sojkher MG, Sojkher EM, et al. E.M.Soikher's hyperoxygenated agent for venous blood oxygen saturation. Patent RU2538662C1, 10.01.2015.
	Hydrogen peroxide solutions for injection into tissues for ischemia or hypoxia
3	Urakov AL. Lympho-subsitute is used to maintain the viability of organs and tissues locally in hypoxia and ischemia. Patent RU2586292C1, 10.06.2016.
	Hydrogen peroxide solutions for ingestion
4	Urakov AL, Urakova NA, Nikitjuk DB. Agent for increasing resistance to hypoxia. Patent RU2604129C2, 20.08.2016.
5	Urakov AL. Energy drink. Patent RU2639493C1, 21.12.2017.
6	Urakov AL. This means physical endurance increases. Patent RU2634271C1, 24.10.2017.
7	Urakov AL, Urakova NA, Gurevich KG, Stolyarenko AP, Samorodov AV. Способ внелегочной оксигенации крови. Application RU2020120367A, 2020.06.15. *Изобретения. Полезные модели*. (Russia). 2021: 35.
	Hydrogen peroxide solutions for inhalation
8	Samylina IA, Ales MYu, Urakov AL, Urakova NA, Nesterova NV, et al. Aerosol for inhalations in obstructive bronchitis. Patent RU2735502C1, 03.11.2020.
9	Urakov AL, Urakova NA. Aerosol for invasive mechanical ventilation in COVID-19. Patent RU2742505C1, 08.02.2021.
	Hydrogen peroxide solutions for intrapulmonary injection
10	Ураков А.Л., Уракова Н.А., Решетников А.П., Ягудин И.И., Сунцова Д.О., Светова М.Д., Столяренко А.П. Способ оксигенации легких при COVID-19. Application RU2021102618A, 04.02.2021. *Изобретения. Полезные модели*. (Russia). 2022:22.

Number in order	Authors, title of invention, number of patent or application, date of the patent publication or registration of the application
11	Urakov AL, Urakova NA, Shabanov PD, Gurevich KG, Fisher EL, et al. Warm alkaline solution of hydrogen peroxide for intrapulmonary injection. Patent RU2807851C1, 21.11.2023.
12	Urakov AL, Urakova NA, Fisher EL. Oxygenated warm alkaline solution of hydrogen peroxide for intrapulmonary injection. Application RU2023128553C1, 02.11.2023.
13	Urakov AL, Shabanov PD. An alkaline solution of hydrogen peroxide and a method of its application to eliminate blood asphyxia. RU2831821C1, 16.12.2024
14	Urakov AL, Shabanov PD. Method of endobronchial injection of drug for emergency elimination of asphyxia. RU2833321C1, 17.01.2025.

By now, it has been established that many normal and pathological tissues of humans and animals contain catalase, which decomposes hydrogen peroxide into water and molecular (gaseous) oxygen at a tremendous rate [27]. It has been reported that the rate of decomposition of hydrogen peroxide by catalase depends on the concentration of catalase and hydrogen peroxide, as well as on pH and local temperature [28,29]. A calculation was also carried out, which showed how much oxygen gas can be formed by splitting hydrogen peroxide. In 2014, 100 ml of 6% hydrogen peroxide solution was shown to release 1.97 liters of molecular oxygen weighing 2.816 g [30]. In other words, 1 liter of 3% hydrogen peroxide solution can produce about 10 liters of gas oxygen.

At the same time, the culmination of research on the oxygen-producing antihypoxic potential of hydrogen peroxide came after March 2020, when the World Health Organization announced the beginning of a pandemic of new coronavirus infection. In particular, from 2020 to 2024, 8 inventions were developed in which various alkaline hydrogen peroxide solutions were proposed as oxygen-producing antihypoxants to prevent hypoxic damage to brain cells in hypoxemia. The analysis of the inventions showed that significant progress in understanding the oxygen-producing antihypoxic activity of hydrogen peroxide solutions had been achieved by considering the factors of physical-chemical interaction during the local application of the drugs. To date, it has been established that warm alkaline hydrogen peroxide solutions (WAHPSs) are the leaders in oxygen enrichment of the respiratory tract and blood among liquid antihypoxic drugs that produce oxygen [16-18].

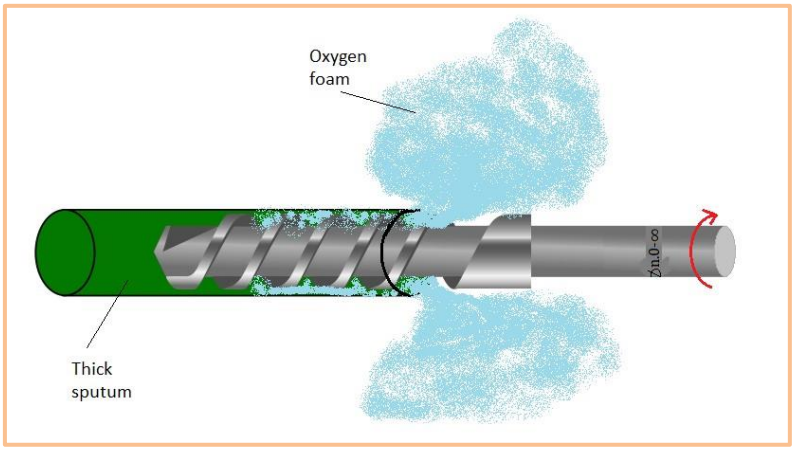

Figure 1. The effect of a warm alkaline hydrogen peroxide solution on the respiratory tract filled with sputum, mucus, pus, and/or blood resembles punching a hole in a wall with a drill bit of perforator.

It was discovered that WAHPSs, when interacting locally with liquid colloidal tissues containing the enzyme catalase, rapidly produced oxygen gas, which quickly formed gas bubbles in colloidal liquids. The process of creating oxygen gas bubbles in liquids resembled a cold booting process that turned colloidal liquids into oxygen foam. It has been shown that

the rapid foaming of sputum, mucus, pus, blood, and/or meconium during endotracheal, endobronchial, and/or intrapulmonary injection of WAHPs may act as a gas-forming airway washer (perforator) and blood oxygenator (through the lungs) (Figure 1) [18].

Thus, respiratory obstruction, hypoxemia, and death from hypoxic damage to brain cells in older people with COVID-19 may sometimes be caused by blockage of the respiratory tract with colloidal fluids such as sputum, mucus, serous fluid, pus, and/or blood. These colloidal liquids contain the enzyme catalase. Therefore, oxygen gas is formed when they interact directly with WAHPSs since catalase decomposes hydrogen peroxide into water and oxygen. The rapid catalase production of oxygen from hydrogen peroxide "exploded" colloidal liquids and turned them into oxygen-rich foam. Based on these results, the authors suggested that endotracheal, endobronchial, and/or intrapulmonary local application of WAHPSs may offer new possibilities of oxygenating the blood without traditional lung ventilation in case of airway obstruction by sputum, mucus, pus, and blood.

3. Mechanism of Mucolytic, Expectorant, Pyolytic, and Airway-Washing Effect of WAHPSs in Airway Obstruction by Sputum, Mucus and/or Pus

Standard solutions of 3-6% hydrogen peroxide (H_2O_2) have been successfully used as antiseptics worldwide to prevent and treat various infectious diseases for more than 100 years [31]. These solutions of hydrogen peroxide belong to safe over-the-counter drugs and are used to treat abrasions and wounds in domestic conditions, as well as for the treatment of chronic wounds. The fact is that their antimicrobial and antiviral activity is still beyond doubt, although they have been used for a very long time, without determining the type of infectious pathogens and their resistance to H_2O_2 and without focusing on the temperature and pH of hydrogen peroxide solutions [32]. However, the authors make no secret that the medical potential of hydrogen peroxide has still not been fully disclosed.

The study of H_2O_2 solutions as medicinal preparations with the potential of expectorant, pyolytic, hemolytic, and washing of airways and chronic wound surfaces due to catalase cleavage into water and oxygen gas began in December 2000. During this period of time, the first patent application was registered, which was entitled "A way of treating long-term non-healing wounds" (RU2187287C1, 20.08.2002) (Table 2). The fact is that this invention clearly showed the advantage of the therapeutic effect of a solution of 3% hydrogen peroxide in the treatment of chronic wounds after alkalizing the solution to pH 8.4 and heating it to +37 -+42°C [33].

Table 2. Inventions in which the local application of warm alkaline hydrogen peroxide solutions (WAHPS) has been proposed for the dissolution and oxygen foaming of pus and other thick colloidal masses.

Number in order	Authors, title of invention, number of patent or application, date of the patent publication or registration of the application
WAHPSs for surface irrigation of purulent wounds	
1	Strelkov NS, Urakov AL, Korovyakov AP, Urakova NA, Kravchuk AP, Korepanova MV, Boyarintseva AV. A way of treating long-term non-healing wounds. RU2187287C1, 20.08.2002.
2	Urakov AL, Urakova NA, Chereshnev VA, Chereshneva MV, Gavrilova TV, Tolstolutskij AJu, Dement'ev VB, Kasimov RH. Softening agent for thick and viscous pus. RU2360685C1, 10.07.2009.
3	Bondarenko LV, Urakov AL, Novikov VE, Zabokritskij NA, Vinogradov AV, Kashkovskij ML, Viter VI, Vavilov AJu, Gajsina LF, Livane RL, Krivopalov SA. Multipurpose solution for epibulbar instillations RU2452478C1, 10.06.2012.
Hypergassed WAHPSs for irrigation of various surfaces	
4	Chereshnev VA, Strelkov NS, Urakov AL, Urakova NA, Mikhajlova NA, Vatulin VV, Shchinov JuN, Dement'ev VB. Hyper-gassed and hyper-osmotic antiseptic mixture. RU2331441C1, 20.08.2008.
5	Kasatkin IA, Urakov AL, Lukoyanov IA, Gabdrafikov RR, Gabdrafikov DR. Aerated mouthwash. RU2635992C1, 17.11.2017.

Number in order	Authors, title of invention, number of patent or application, date of the patent publication or registration of the application
6	Urakov AL, Reshetnikov AP, Gadelshina AA. Bleaching cleaner of dentures. RU2659952C1, 04.07.2018.
7	Urakov AL, Shabanov PD, Alies MYu. Method of using plaque removal solution with irrigation agent. RU2723138, 09.06.2020.
WAHPSs for injection	
8	Urakov AL, Urakova NA, Otvagin IV, Strelkov NS, Novikov VE, Jushkov BG, Mal'chikov AJa, Subbotin AV, Gajsina LF. Method and means for removal of the sulfur plug. RU2468776C2, 27.06.2012.

It was shown that in patients with pressure sores (compression ulcers) in chronic wounds, rapid formation of granulation tissue occurred 2-3 days and wound healing 1-2 weeks after the start of wound treatment with WAHPSs. It has been reported that irrigation of wounds with WAHPSs softened purulent masses and accelerated the catalase cleavage of hydrogen peroxide into water and gas oxygen. At the same time, the rapid release of oxygen gas provided "explosive" destruction of thick purulent masses, oxidative destruction of infectious agents located in purulent masses, and their mechanical removal to the outside, that is, wound cleansing, deodorization and acceleration of aerobic metabolism in granulation tissue cells, which accelerated the healing of chronic wounds.

A few years later, the inventions “Softening agent for thick and viscous pus” (RU2360685C1, 10.07.2009) and “Bleaching cleaner of dentures” (RU2659952C1, 04.07.2018) were created, in which sodium bicarbonate was added to hydrogen peroxide solution for the first time. The authors of the inventions reported that combining hydrogen peroxide with sodium bicarbonate in solution allowed the change of the traditional acid activity to alkaline activity within pH 8.4 and increased the osmotic activity. The arsenal of original hydrogen peroxide and sodium bicarbonate solutions heated to +42°C was then very rapidly expanded, and this group of drugs was named WAHPSs [32]. It has been reported that the moderate hyperthermic, osmotic, and alkaline activity of WAHPSs gives them a unique physical-chemical activity and provides leadership in disinfecting action and dissolving thick, purulent masses. Therefore, the WAHPSs got their second name - "pyolitics" [34,35].

Thanks to the local application of WAHPSs, the phenomenon of physicochemical dissolution of purulent masses was discovered by the process of formation of oxygen gas bubbles in them (by analogy with cold boiling). It remained to take one step so that oxygen gas was also included in the group of pyolytics. This step was taken: gas oxygen was converted to pyolytics by introducing oxygen into WAHPSs at overpressure. The proposal to enrich WAHPSs with oxygen gas under high pressure was first used in the development of a bleaching agent designed for cleaning dentures from plaque, traces of pus, and blood (RU2659952C1, 04.07.2018) [36]. The authors of the invention have shown that the presence of oxygen gas dissolved under overpressure in hyperoxygenated WAHPS enhances the pyolytic action of the carbonated medicament by increasing its foaming activity. In particular, a solution of 3% hydrogen peroxide and 2 - 10% sodium bicarbonate heated to a temperature of +37 - +42°C, enriched with oxygen gas due to an overpressure of 0.2 atm, has been patented as a denture whitening cleaner [37]. It has been reported that hyperoxygenated WAHPSs in local interaction with purulent masses have a more pronounced disinfectant and pyolytic effect and significant bleaching, deodorizing, and antihypoxic effects. It was shown that at local application the above pharmacological activity of hyperoxygenated WAHPSs is achieved due to hyperthermic softening of dense purulent masses (and other colloidal biological masses), alkaline saponification of lipid and protein-lipid complexes that form the basis of thick sputum, mucus, pus and blood, as well as due to cavitation loosening of thick colloidal masses by oxygen gas bubbles, their dissolution and oxidative discoloration [38,39]. However, for the sake of

historical reference, it should be pointed out that 10 years earlier, for hypergasification of pyolytics, inventors used not oxygen gas but carbon dioxide gas under overpressure (RU2331441C1, 20.08.2008). In addition, in 2017, a patent for the so-called "Aerated mouthwash" (RU263599992C1, 17.11.2017) was obtained, in which it was proposed to enrich the drug solution with another inert gas, in particular, helium (Table 2).

Consequently, WAHPSs can be enriched with oxygen gas by introducing gas into them under increased pressure, i.e., they can be converted into hyperoxygenated WAHPSs. Overpressure increases the concentration of oxygen gas in the drug solution, which, under lower pressure conditions (including 1 atm pressure), begins to release oxygen gas without the participation of catalase and hydrogen peroxide. In this process, oxygen gas bubbles appear in the drug solution, which resembles the cold boiling process. This process is similar to the release of carbon dioxide bubbles in carbonated beverages after opening the bottles of carbonated beverages. Therefore, the invention of hyperoxygenated WAHPSs proved the successful physicochemical conversion of gaseous oxygen into pyolytics, which provided a truly revolutionary way to eliminate hypoxemia in respiratory obstruction not only by sputum, mucus, pus, blood, and other colloidal fluids rich in the enzyme catalase but also by other fluids devoid of catalase. The fact is that endotratracheal, endotrabronchial, and/or intrapulmonary injection of hyperoxygenated WAHPSs increased airway oxygen content through catalase-mediated hydrogen peroxide breakdown and without it. Therefore, intrapulmonary hyperoxygenated WAHPS showed a revolutionary way to oxygenate the blood, which may become an alternative to conventional artificial lung ventilation and ECMO for acute respiratory distress syndrome in the final stage of COVID-19.

4. Mechanism of Oxygen-Producing Effect of Intrapulmonary Injection of WAHPS in Airway Obstruction by Blood

The cause of airway obstruction and hypoxemia may be the accumulation of sputum, mucus, and pus in the bronchi and bronchioles and the appearance of blood in them [16,18,40-48]. It is reported that one of the causes of blood in the airway may be pulmonary hemorrhage, and hemoptysis may be a symptom of pulmonary hemorrhage and blood in the airway [49-53]. The most common cause of hemoptysis is infectious diseases of the lungs and respiratory tract, such as tuberculosis, as well as lung cancer [54-57]. Suffocation caused by blood asphyxia is a lethal condition because, in this case, ventilation of the lungs with oxygen gas does not ensure its absorption into the blood. Therefore, in sudden asphyxia by blood, to eliminate hypoxemia, it is very important to have drugs that can immediately increase the oxygen content in the respiratory tract and the blood of the patient when applied intrapulmonary. The fact is that blood asphyxia requires immediate medical attention. Unfortunately, pulmonologists and resuscitators do not have drugs that can immediately turn blood, blood clots, and streaks of blood in the mucus in the respiratory tract into oxygen foam and provide due to this urgent oxygenation of blood through the respiratory organ [44,58-61]. Nevertheless, the search and development of such drugs is underway [18,62].

The patent for the first invention, the essence of which was the action of a solution of H_2O_2 on a portion or clot of blood, taking into account the catalase cleavage of hydrogen peroxide into water and oxygen gas, was granted in December 2006 (Table 3). This invention was intended for washing the vaginal cavity in women with massive postpartum bleeding during vaginal delivery. In this invention, a solution of 3% hydrogen peroxide heated to +42 - + 45°C was used, with a pH of less than 7.0. That is, the solution had acidic activity. Then, in

2009, a patent was granted for an invention for treating hemothorax. In this invention, injection into a clot of coagulated blood of a solution of 5% sodium bicarbonate and 1.5% hydrogen peroxide heated to +37°C was first proposed for emergency dissolution of a blood clot in the pleural cavity. In other words, the injection of warm alkaline hydrogen peroxide solution into the blood clot was first proposed to dissolve the blood clot urgently. It has been shown that the blood clot is converted into an oxygenated foam immediately after a single injection of a warm alkaline hydrogen peroxide solution into a blood clot located within the pleural cavity.

Table 3. Inventions in which the local application of WAHPS has been proposed for dissolving and discoloring blood clots and spots, as well as for foaming a blood clot with oxygen inside the respiratory tract during blood asphyxiation.

Number in order	Authors, title of invention, number of patent or application, date of the patent publication or registration of the application
WAHPS for local interaction with blood within body cavities	
1	Urakova NA, Urakov AL, Sokolova NV, Halimov PK. Method for interrupting uterine hemorrhage. RU2288656C1, 10.12.2006.
2	Urakov AL, Mal'chikov Aja, Shchinov JuN, Urakova NA, Tarasov SL,Zabokritskij NA. Methods of diagnostics and treatment of clotted hemothorax by AY Malchikov. RU2368333C1, 27.09.2009.
WAHPSs for localized interaction with blood clots and blood stains on clothing and dressings	
3	Reshetnikov AP, Urakov AL, Urakova NA, Mikhajlova NA, Serova MV, Elkhov IV, Dement'ev VB, Zabokritskij NA, Sjutkina JuS. Method of express cleaning of blood stains off clothes. RU2371532C1, 27.10.2009.
4	Urakova NA, Urakov AL, Urakova TV, Gadelshina AA. Bleaching opener of dried blood for wrapping bandages adhered to a wound. RU2653465C1, 08.05.2018
WAHPS for discoloration of a hematoma under the nail	
5	Urakov AL. Method for whitening of sore under nail. RU2631592C1, 25.09.2017
6	Urakov AL, Urakova NA, Gadelshina AA, Gabdrafikov RR, Gabdrafikov DR. Method for blue nail treatment. RU2641386C1, 17.01.2018
WAHPS for injections to discolor bruises	
7	Urakov AL, Urakova NA, Chernova LV, Fisher EL. Bleach bruising. RU2539380C1, 20.01.2015
8	Urakov AL, Urakova NA. Bleaching agent. RU2589682C1, 10.07.2016
9	Urakov AL, Urakova NA, Kasatkin AA, Chernova LV, Nasyrov MR, Fisher EL. Method for skin discoloration in bruising area. RU2586278C1, 10.06.2016.
10	Urakov AL, Urakova TV. Agent for intradermal bruise whitening. RU2573382C1, 20.01.2016
11	Urakov AL, Urakova NA, Nikitiuk DB, Chernova LV. Method of skin discoloration in the area of bruising. RU2582215C1, 20.04.2016
12	Gots IR, Urakov AL, Urakova NA, Reshetnikov AP, Gabdrakhmanova LD, Bajmurzin DYu. Method of removing paint from skin. RU2600504C1, 20.10.2016.
13	Urakova NA. Urakov AL, Gabdrafikov RR, Gabdrafikov DR, Gadelshina AA. Method for emergency bleaching and blood crust removal from the skin in place of squeezed-out acne. RU2631593, 25.09.2017.
14	Urakova NA, Urakov AL, Urakova TV, Gadelshina AA, Bannikov AO. Method for whitening of a bruise under the eye. RU2639283, 20.12.2017
15	Urakova NA, Urakov AL, Urakova TV, Kasatkin AA, Reshetnikov AP. This means for intravital skin whitening near blue eyes. RU2639485, 21.12.2017
16	Urakov AL. Decolorant of blood. RU2647371, 15.03.2018
17	Urakova NA, Urakov AL. Method of emergency bleaching of skin hematoma under the eye. RU2679334, 07.02.2019

Also, in 2009, a patent was obtained for an invention that was developed for emergency bleaching of blood stains on clothing (RU2371532C1, 27.10.2009). This invention was again based on WAHPS, which was found to rapidly dissolve and decolorize stains and traces of blood on clothing. This was possible due to the rapid release of oxygen gas, which appeared due to the presence of the enzyme catalase in fresh and old bloodstains [32,34,37,63].

Thanks to this invention, a new direction in pharmacology was born - the development of new drugs designed for oxygen decolorization of traces and blood stains on textiles, clothing, bandages, dressings, wound surfaces, and even in the skin, namely in the area of bruises [64].

Despite such a revolutionary proposal and its effectiveness in discoloring stains and traces of blood on clothes and fabric, this invention has remained unnoticed by the medical community. Under these circumstances, the authors independently continued research in this

direction and, after 9 years, received another patent for an invention developed for the safe removal of bloody bandages adhered to wounds and named “Bleaching opener of dried blood for wrapping bandages adhered to a wound” (RU2653465C1, 08.05.2018).

The discovered ability of gaseous oxygen, vigorously released by the cleavage of hydrogen peroxide under the action of the enzyme catalase, to decolorize blood and its traces at the local application of WAHPSs was the basis for 2 inventions developed in the same period of time for urgent discoloration of hematomas under the nail: “Method for whitening of sore under nail” (RU2631592C1, 25. 09.09.2017) and “Method for blue nail treatment” (RU2641386C1, 17.01.2018). The authors showed that injection into the hematoma area of a solution of 3% hydrogen peroxide and 10% sodium bicarbonate heated to the temperature of +37 - +42°C provided immediate rapid release of oxygen gas, blood foaming, and its transformation into white foam. At the same time, injection of WAHPS under the nail plate in the area of subnail hematoma, carried out under the control of nail color dynamics, provided complete whitening of the subnail hematoma with a single application of the drug.

As can be seen from Table 3, in the following years, 11 other inventions involving WAHPSs were developed. This group of inventions was developed for intradermal injections for the purpose of effective and safe skin discoloration in the area of bruises. A review of the claims of these inventions shows that all WAHPSs intended for injection include hydrogen peroxide in the concentration range of 0.01-0.03% and sodium bicarbonate in the concentration range of 1.7 - 1.8%. All WAHPSs are heated to a temperature of +37 - +42°C before injection. These inventions disclosed that it is such a range of concentrations of said ingredients that provide safe and effective injections of WAHPSs into the region of them with the physicochemical activity necessary to effectively and safely decolorize bruises [64,65]. Specifically, it is such WAHPSs that have the following physicochemical activity:

- oxygen-producing activity of WAHPSs in the process of catalase cleavage of hydrogen peroxide at the “right” intensity to decolorize hemoglobin and all its colored metabolites and to preclude the formation of gas bubbles, i.e., to preclude embolization of blood vessels,

- alkaline activity of WAHPSs with pH 8.4 and the process of alkaline saponification of lipid and protein-lipid complexes of fresh and old blood, providing washing activity and effective washing of skin from traces of blood and hemoglobin metabolites,

- isotonic activity in the range of 280 - 300 mosmol/l of water.

Consequently, the accumulation of blood in the airways may be a cause of asphyxia independent of other factors, including COVID-19 [66-70]. Analysis of the contents of the cited inventions has shown that the enzyme catalase has greater biochemical activity not only in fresh portions of blood but also in “old” blood spots and clots. Moreover, the contents of the cited inventions indicated that the presence of fresh blood or streaks of old blood in the airways as part of sputum (bloody sputum), mucus, and/or pus does not reduce the intensity of catalase cleavage of hydrogen peroxide into water and oxygen gas during topical (endotracheal, endobronchial and/or intrapulmonary) injection of WAHPSs. In other words, intrapulmonary WAHPSs provided optimal conditions for the interaction of catalase enzyme with hydrogen peroxide and its intensive metabolism to oxygen gas in the presence of blood in the respiratory tract.

This conclusion is supported by laboratory and experimental studies performed with isolated portions of sputum, mucus, and blood from mongrel rabbits and humans [34,71-73]. The authors reported that local interaction of WAHPSs with portions of fresh blood or old

blood clots and/or spots of “old” (dried) blood is immediately manifested by the rapid transformation of blood and its residues into a fluffy white oxygen foam.

Moreover, studies of the dynamics of the local temperature of sputum, mucus, pus, and blood during local interaction with hydrogen peroxide solution in the infrared range of the radiation spectrum using a thermal imager were conducted. The results of these studies showed that the direct interaction of hydrogen peroxide solution with a portion of blood at an equal initial temperature immediately increased the local temperature of the oxygen foam produced by their interaction with each other [74,75]. Based on the findings, the authors concluded that the interaction of hydrogen peroxide with blood is a variant of an exothermic reaction. In all likelihood, the following occurs: hydrogen peroxide is metabolized to oxygen gas, after which oxygen gas begins to participate in oxidative reactions accompanied by heat release. On this basis, the authors suggested that hydrogen peroxide may influence the heat generation process in cells and participate in the formation of human temperature homeostasis [75].

5. Discussion

Solutions of 3-6% hydrogen peroxide have been used in medicine as antiseptics for over 100 years. Throughout this period of time, a distinctive feature of hydrogen peroxide solutions was that quality hydrogen peroxide solutions had only acidic activity, i.e., had a pH value of less than pH 7.0. The acid activity of hydrogen peroxide solutions was included in the controlled indicators of drug quality. Only at the beginning of the 21st century, thanks to Russian researchers, it was established that the acid activity of hydrogen peroxide solutions is an inhibitor of their biological activity in local applications. The acid activity of hydrogen peroxide solutions was the main brake in expanding the scope of medical application of H_2O_2 [18,32,62]. Plus, it has been reported that another inhibitor in the progress of the medical application of hydrogen peroxide solutions in the role of oxygen gas donator was their temperature between +24 - +26°C.

More than 20 years of efforts by pharmacologists have culminated in a revolutionary change in the physical-chemical properties of hydrogen peroxide solutions. It was proved that hydrogen peroxide solutions with ingredient concentration from 0.01 to 3% at temperature +37 - +42°C and alkaline activity with pH value pH 8.4 (due to combination with sodium bicarbonate in the range of 1.7 - 10%) acquire optimal oxygen-producing antihypoxic, pyolytic, mucolytic and hemolytic activity at local application. In doing so, they have generated 39 inventions addressing the above medical problems (Tables 1-3). The arsenal of drugs developed was called “warm alkaline hydrogen peroxide solutions” (WAHPSs) [17,18,39]. In the process of developing a new group of drugs, namely oxygen-producing antihypoxants, it was found that 1 L of a 6% hydrogen peroxide solution can metabolize into 20 L of oxygen gas [30]. As a result of these efforts, researchers around the world have been able to significantly advance the understanding of the mechanism of local action of hydrogen peroxide and expand the scope of H_2O_2 application, including the urgent metabolism of H_2O_2 to O_2 by the tissue enzyme catalase [3,36,62].

The powerful oxygen-producing activity of WAHPSs prompted researchers to repurpose H_2O_2 from antiseptics into pyolytics, mucolytic, hemolytic, expectorant, and oxygen-producing antihypoxants [34,35,76,77]. Thanks to years of systematic, focused research and careful analysis of their findings, researchers exploited the opportunity they discovered to use intrapulmonary WAHPSs as an alternative to intrapulmonary breathing gases, including oxygen gas, used universally in artificial lung ventilation and extracorporeal

membrane oxygenation (ECMO) [3,12-19,78-88]. The catalyst for these studies was the new coronavirus infection, the COVID-19 pandemic. It is no secret that the final stage of COVID-19 in older adults can end tragically because of hypoxic brain cell damage due to ARDS [89-91]. In turn, ARDS can be caused by airway obstruction by sputum, mucus, and pus with blood streaks [92]. It is important to remember that these colloidal fluids are highly viscous. Therefore, they cannot be quickly removed from the respiratory tract with standard expectorants and mucolytics, which are also deprived of antihypoxic oxygen-producing activity [18]. In addition, it should be taken into account that the medical standard does not contain drugs intended for intrapulmonary injection of solutions that immediately produce oxygen and turn colloidal liquids into fluffy oxygen foam [62].

A paradoxical situation exists in the emergency medical care provided to patients with ARDS in the final stage of COVID-19. There is no doubt that the cause of death in COVID-19 patients is not coronavirus brain cell damage but hypoxic brain cell damage [3,4,12,17,18,72]. Hypoxic brain cell damage develops due to excessively severe and prolonged hypoxemia caused by asphyxia caused by respiratory obstruction [39,73,93-100]. At the same time, the emergency medical care provided worldwide by medical professionals in ambulances and intensive care units of medical hospitals for asphyxiation caused by airway obstruction by thick and viscous sputum, mucus, pus, and blood in elderly COVID-19 patients is performed using the same techniques as in mature patients while maintaining airway patency for respiratory gases [17,18,62,92].

It is surprising, but it so happens that in severe hypoxemia in COVID-19 patients with asphyxia due to airway obstruction, physicians use artificial lung ventilation (ALV) technology that promotes blood oxygenation only when the airway remains passable for the administered oxygen gas. Therefore, the ALV technology used does not provide highly effective blood oxygen saturation for airway obstruction in COVID-19. And physicians are aware of this. However, their actions are justified in the current situation because the researchers have not armed them with any alternative other than ECMO [101-106]. The facts are that in the COVID-19 pandemic, the most common ventilators were insufficient to provide emergency care for all patients with severe suffocation. Therefore, to save patients' lives in the final stage of COVID-19, it was even suggested that a single ventilator could be used to ventilate 2- patients simultaneously [107,108]. Other researchers have reported the need to design futuristic telemedicine using artificial intelligence and robotics in the COVID-19 era [109-112].

At the same time, the ideas about the important role of cytokine storm in the pathogenesis of respiratory failure and ARDS in COVID-19, especially in elderly patients, are gradually receding into the background. The fact is that the low efficacy of steroidal and non-steroidal anti-inflammatory drugs has dispelled the myth about the high importance of this link of pathogenesis in the development of suffocation, hypoxemia, and death in the final stage of COVID-19 [113- 118]. This conclusion also proves the lack of expected efficacy of available vaccines, especially in older adults [119-125]. The hopes of physicians and researchers associated with chemotherapeutic agents have also failed in COVID-19 [126-129].

Realizing that anti-inflammatory drugs, chemotherapeutic agents, and vaccines are fundamentally unable to increase blood oxygenation in hypoxemia, while oxygen gas is the true number one antihypoxant for hypoxemia and is capable of not only eliminating hypoxemia but also causing hyperxemia, we have no choice in the fight against hypoxemia. Indeed, until recently, it was believed that only one drug was capable of eliminating hypoxemia, and that was oxygen gas [130-135]. Unfortunately, the efficacy of oxygen administered by conventional

ALV is still low, with airway obstruction caused by sputum, mucus, pus, and blood. The use of oxygen gas for blood saturation with ECMO also cannot become the standard of emergency medical care for acute airway obstruction (for sputum, mucus, pus, or blood asphyxia) because ECMO cannot be used in all ambulances and all intensive care units of medical hospitals in all countries of the world. In addition, ECMO remains a difficult-to-access, expensive, and very dangerous blood oxygenation technology for most people, even in the United States [136-144].

Under these circumstances, the report that in cases of excessive accumulation of sputum, mucus, pus, and/or blood in the airways and the development of excessively severe and prolonged hypoxemia, the threat of hypoxic damage to the first cortical cells can be relieved in seconds through the use of hydrogen peroxide, and more specifically WAHPSs and their intrapulmonary injections, is revolutionary [3]. At first approximation, it seems incredible since hydrogen peroxide has long been used in medicine. However, a close examination of the arsenal of WAHPSs and the prospects for intrapulmonary injections very quickly leads one to believe in this fantastic proposition. Analysis of known drug products showed that there is still no drug solution developed exclusively for intrapulmonary injection in the world. Moreover, WAHPS developed for intrapulmonary injection (RU2807851C1, 21.11.2023) is the world's first oxygen-producing antihypoxant designed specifically for injection into the respiratory organ to increase blood oxygenation through the lungs [18,62].

It's amazing, but simply injecting a certain WAHPS into any selected body part provided immediate oxygen gas to that part of the body without ventilating the lungs or supplying that part with arterial blood! This is fully applicable to airways filled with phlegm, mucus, pus, and/or blood, as almost all human body tissues contain catalase, which speeds up the metabolism of hydrogen peroxide to oxygen gas millions of times over [18,62,145-147].

Experimental studies of the effectiveness of oxygen-producing antihypoxic action of different hydrogen peroxide solutions have been carried out with isolated organs and tissues of animals and humans, live aquarium fish, and mongrel rabbits [3,12-19148-150]. The results obtained in this case convince that hydrogen peroxide injected as part of WAHPSs into various tissues containing the enzyme catalase is likened to a kind of suicide since hydrogen peroxide immediately metabolizes into oxygen gas and water. In particular, a single intrapulmonary injection of WAHPS at complete occlusion of rabbit airways with artificial sputum provides immediate conversion of hydrogen peroxide into oxygen, filling the lumen of bronchi, bronchioles, and alveoli with oxygen gas and in 10 - 12 seconds eliminates hypoxemia [3].

Thus, there is every reason to assume that a promising area of search and development of new drugs - oxygen gas producers - has been opened. Oxygen gas as a metabolite of hydrogen peroxide has already entered the arsenal of oxygen-producing antihypoxants in the form of WAHPSs, which accelerate the healing of chronic wounds [32]. It is expected that in the near future, WAHPSs may significantly displace meat fly larvae from the medical standard of treatment of chronic wounds [35].

However, we still have a lot of research to do to understand all aspects of local application of the invented WAHPSs, especially in inhalation and intrapulmonary injections in both experimental and clinical settings. Therefore, comprehensive large-scale studies are needed to draw definitive conclusions. It is hoped that an active study of the topical application of WAHPSs as oxygen prodrugs antihypoxants may optimize their use in combating hypoxic and ischemic cell damage, especially under conditions of low ventilation efficiency with respiratory and oxygen gas.

6. Conclusions

A review of scientific articles and inventions has shown that an active study of the possibility of developing new oxygen-producing antihypoxants by physical-chemical repurposing of hydrogen peroxide has begun in recent years. Information analysis revealed 39 inventions, the essence of which formed the basis for forming a new group of drugs, namely, warm alkaline hydrogen peroxide solution. Hydrogen peroxide, sodium bicarbonate, and water were shown to be the main ingredients of the new generation of antihypoxants. It was reported that the mechanism of action of WAHPSs is fundamentally different from all known antihypoxants. First, the new-generation antihypoxants were very promising for blood oxygenation through the lungs by local intrapulmonary application. Second, the target of the effect of WAHPSs was catalase contained in sputum, serous fluid, pus, and blood. The results of the first experimental and clinical studies showed that due to the catalase decomposition of hydrogen peroxide into water and molecular oxygen, intrapulmonary WAHPSs generated oxygen gas with high intensity inside the airways when they were obstructed by colloidal fluids containing the enzyme catalase. These results allowed the inventors of the inventions to suggest that in the near future, intrapulmonary WAHPSs may become the leading drugs for emergency relief of acute severe hypoxemia caused by complete airway obstruction by sputum, serous fluid, pus, and blood.

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Conflicts of Interest

The authors declare no conflict of interest.

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