12

Using Ozone Therapy as an Option for Treatment of COVID-19 Patients: A Scoping Review

Sarvin Radvar, Sepideh Karkon-shayan, Ali Motamed-Sanaye, Mohammadreza Majidi, Sakineh Hajebrahimi, Negar Taleschian-Tabrizi, Fariba Pashazadeh, and Amirhossein Sahebkar

Abstract

Recent investigations are seeking a novel treatment to control the new pandemic of coronavirus 19 (COVID-19). The aim of this systematic review was to study the effect of ozone therapy on COVID-19 patients and the available supporting evidence. Electronic databases including MEDLINE (via PubMed), EMBASE, Cochrane Library (CENTRAL), and TRIP, clinical trial registries, and preprint sources were searched for published evidence-based articles. In addition, manual searching was conducted for articles published up to April 6, 2020, using MeSH and free text keywords with no language limitation. Articles were screened, categorized, and extracted for relative data. Data were reported in a descriptive manner. Among 234 articles, 9 were selected for review of the inclusion criteria. No published original articles were found regarding the efficacy of ozone therapy on COVID-19. Five review studies were found in which the potential role of systemic ozone therapy was concluded to be effective in controlling COVID-19 because of its antiviral, oxygenation, anti-inflammatory, oxidation balancing, and immunomodulation effects. Three ongoing clinical trials were registered in China. A preliminary report of an ongoing study in Italy on 46 patients (11 intu-

S. Radvar
Research Center for Evidence-based- medicine, Iranian EBM Center: A Joanna Briggs Institute Affiliated Group, Tabriz University of Medical Sciences, Tabriz, Iran

Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran

S. Karkon-shayan (✉) · A. Motamed-Sanaye
M. Majidi
Student Research Committee, Gonabad University of Medical Sciences, Gonabad, Iran

S. Hajebrahimi · F. Pashazadeh
Research Center for Evidence-based- medicine, Iranian EBM Center: A Joanna Briggs Institute Affiliated Group, Tabriz University of Medical Sciences, Tabriz, Iran

N. Taleschian-Tabrizi
Research Center for Evidence-based- medicine, Iranian EBM Center: A Joanna Briggs Institute Affiliated Group, Tabriz University of Medical Sciences, Tabriz, Iran

Department of physical medicine and rehabilitation, faculty of medicine, Tabriz University of medical sciences, Tabriz, Iran

A. Sahebkar (✉)
Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran

Applied Biomedical Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
e-mail: sahebkara@mums.ac.ir

P. C. Guest (ed.), *Identification of Biomarkers, New Treatments, and Vaccines for COVID-19*,
Advances in Experimental Medicine and Biology 1327, https://doi.org/10.1007/978-3-030-71697-4_12

bated and 35 non-intubated) showed that in 39 (84%) of the patients, an improvement was seen. In spite of the promising background data, as well as the expert opinions and a preliminary report indicating the effectiveness of ozone, there is still not enough evidence to confirm this as a viable treatment option for COVID-19.

Keywords

Ozone therapy · Autohemotherapy · COVID-19 · SARS-CoV-2 · Systematic review

1 Introduction

Novel coronavirus disease (COVID-19), which is responsible for causing severe acute respiratory syndrome, was first identified in December 2019 in Wuhan and later became a large global outbreak and major public health issue [1, 2]. The disease is caused by SARS-CoV-2, which is an enveloped non-segmented positive-sense RNA virus [3]. This virus causes flu-like symptoms such fever, dry cough, dyspnea, and fatigue. Further reported symptoms are sputum production, headache, hemoptysis, diarrhea, dyspnea, and lymphopenia, as well as gastrointestinal symptoms [4–6]. Pneumonia is the main presentation of the illness ranging from normal O_2 saturation to significant lung injury and hypoxemia due to severe acute respiratory syndrome, which can be life-threatening [7]. Therefore, complementary oxygenation has been applied to save lives.

In the absence of any approved efficient treatment of this new disease, there is a growing interest in testing novel and old methods. In the mid-nineteenth century, ozone therapy was approved in medical community [8]. Ozone is a triatomic oxygen (O_3) that acts as an oxidizing agent and inactivates bacteria, fungus, and viruses as a disinfectant and as a therapeutic approach [8, 9]. Water disinfection, treatment of various infectious diseases, wound healing, and boosting the immune system with minimal side effects are the well-known applications of this therapy [10]. Recent studies have shown that this method has some efficacy in the treatment of pulmonary and vascular diseases [11–13]. The mechanism involves the reaction of ozone with biological substrates leading to the synthesis of signal transducers [10, 14]. It also increases the concentration of oxygenated hemoglobin and improves oxygenation in tissues [15]. This can be an advantage over other treatment options of hypoxic conditions, such as those seen in COVID-19 patients. For these reasons, a number of studies have evaluated the potential of using ozone therapy as a novel treatment for COVID-19 patients.

The objective of this scoping review was to provide a clear understanding of the current evidence regarding ozone therapy as a treatment option for COVID-19. Also, we have briefly reviewed the effects of ozone therapy on other viral infections and respiratory diseases, and investigated the possible mechanisms of actions as it relates to the known effects of COVID-19 disease.

2 Methods

2.1 Inclusion Criteria

All studies and primary reports, which assessed the effects of ozone therapy on COVID-19, were included in this review regardless of study designs. Because of the novelty of the project and the small amount of available data, no exclusion criteria were applied to avoid losing data and maximize comprehensiveness.

2.2 Search Strategy

The search process was done independently by two authors (FP and SR). The electronic databases including MEDLINE (via PubMed), EMBASE, Cochrane Library (CENTRAL), and TRIP were searched for evidence-based articles published until April 6, 2020. In addition, in order to ensure the comprehensive search of clinical trials (unpublished or ongoing), the following databases were searched: clinicaltrials.gov, the Iranian clinical trial registry, the Chinese clinical trial registry, the Italian clinical trial registry, and clinicaltrialsregister.eu. Furthermore, for retrieving unpublished articles, Google scholar was also searched. The main keywords used for the review (Both MeSH or free text) were ozone, ozone therapy, coronavirus, COVID-19, SARS-CoV-2, antiviral, and viral infection. No language limitation was applied, and data other than English were translated using translation websites and applications.

We also searched through the references of the selected papers. Preprint articles were searched via BioRxiv, Medrxiv. Manual searching was also undertaken to ensure comprehensiveness, which involved the use of Google and scientific web pages to obtain further articles and information about this topic. In order to obtain the results of ongoing trials and webpage reports, e-mail messages were sent to authors.

Search results were assembled in EndNote X7 and duplicate references were removed. The first screening was performed on titles and abstracts, and the secondary screening was completed after reviewing full texts to include related articles.

3 Results

3.1 Extraction of Results

All 234 hits from the initial search were screened by title and abstract and 72 studies were selected for further evaluation. Also, relevant studies were included considering the concept of review and the set scopes (Fig. 12.1). Nine studies were obtained concerning both COVID-19 and ozone therapy, including 5 hypothetical reviews with expert opinions indicating potential effects of ozone therapy as a COVID-18 treatment (Table 12.1). Three ongoing clinical trials were registered in China, and a preliminary report of a trial was generated in Italy. No articles with relevant new data were found. Because of the novelty of the issues and to ensure comprehensiveness, related studies, but non-COVID-18-associated, were also reviewed. Along these lines, 7 studies assessing the role of ozone therapy in medicine, in addition to 3 clinical trials on respiratory diseases, were included. In addition, 11 studies recognized the potential role of ozone as a treatment of viral infection. Three clinical trials are currently underway in China to study the effect of ozonated autohemotherapy but no results have been released yet. The information on these trials is listed in Table 12.2.

There have also been primary reports by the Scientific Society of Ozone Oxygen Therapy (SIOOT) in Italian hospitals for the use of oxygen-ozone therapy in the treatment of COVID-19. Based on the second SIOOT report on this therapy applied to 46 patients with confirmed COVID-19 infections, 39 out of 46 (84.7%, including 11 intubated and 35 non-intubated patients), showed improvement of clinical symptoms. Among the patients, the number of extubated patients was 6, 3 were currently intubated, and 28 did not need intubation. Four of the intubated patients died due to bacterial infection, septic shock, pulmonary emboli, or myocarditis. Five patients became free of the virus, as determined by two negative swabs [16–18].

3.2 Protocols

Different protocols are available to supply ozone: major autohemotherapy (MAH); ozonized saline solution (O3SS); extracorporeal blood oxygenation-ozonation (EBOO); and a variant of the minor autohemotherapy (MiAH). All clinical protocols should be defined in accordance with the standard dosage and procedures described in the Madrid Ozone Therapy Report [19].

3.3 Mechanism of Ozone as a Treatment

Ozone is an important gas in nature with high solubility in water. Ozone can be formed from three basic sources of energy-driven reactions: chemical electrolysis, electrical discharge, and ultraviolet light radiation. Based on the findings of numerous scientific studies, ozone has a high

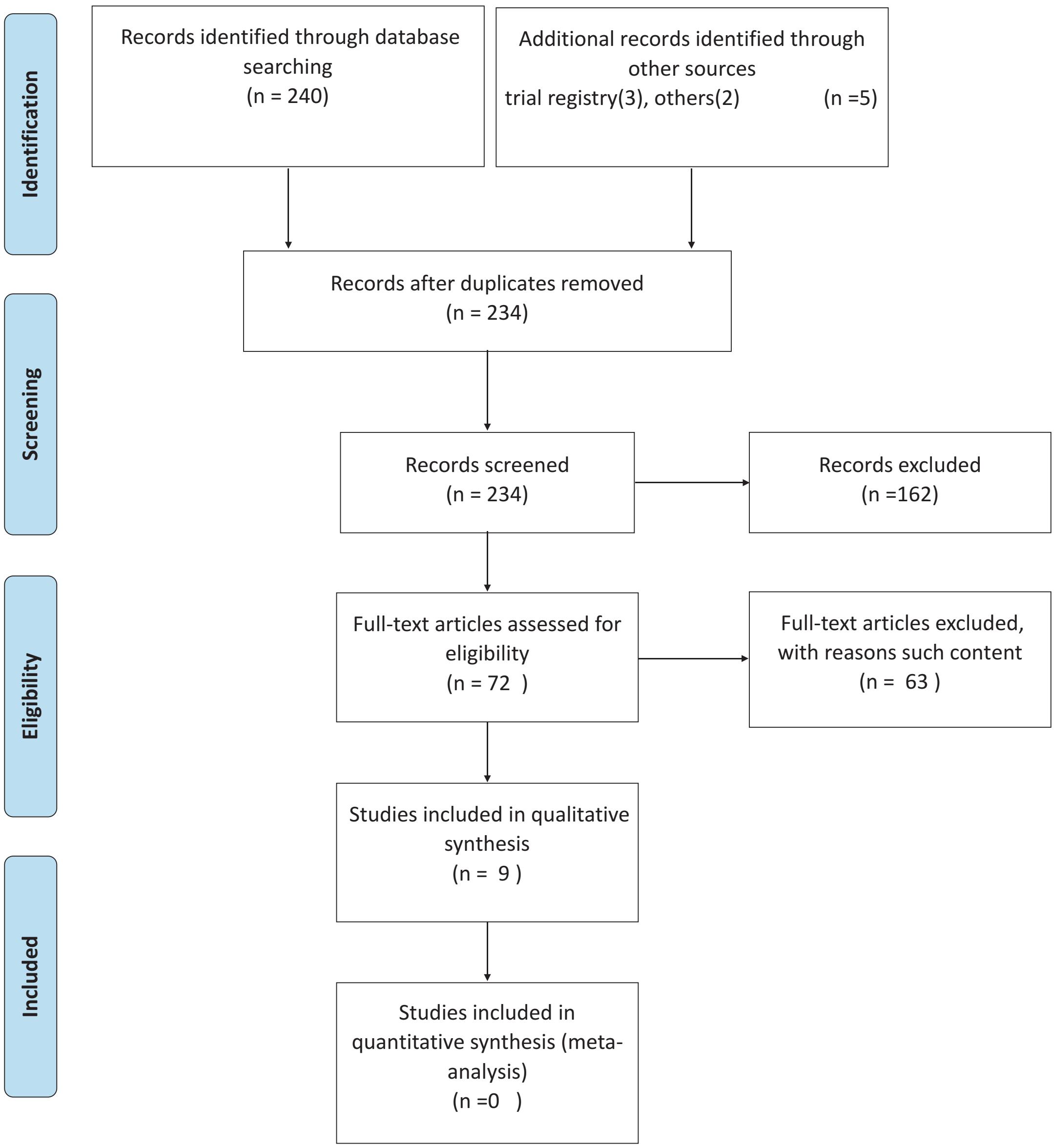

Fig. 12.1 PRISMA flowchart of selection process (Moher 2009)

ability to oxidize substances. The biological basis of ozone therapy is its reaction with proteins, amino acids, and unsaturated fatty acids, which are found in blood and cell membranes. The four fundamental products of this action are ozonides, aldehydes, peroxides, and hydrogen peroxide [20]. The interaction of ozone with unsaturated cell membrane fatty acids in the intestinal mucosa (rectal administration) or blood cells (in the extracorporeal blood–ozone mixture, during autohemotherapy) produces aldehyde and hydroxy-hydroperoxide (ozone-peroxide), which forms H_2O_2 and second aldehyde—4-hydroxynonenal (4-HNE). These substances act as second messengers and prompt a further adaptive response [21, 22]. If ozone is used at specific therapeutic doses, it stimulates nuclear factor erythroid 2-related factor 2 (NRF2) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and balances the antioxidant

Table 12.1 Characteristics of published articles on COVID-19

References	Year	Country	Aims and purpose	Type of study	Key findings
Galoforo et al. [31]	2020	Italy	Indicate the potential effects of ozone as a COVID-19 treatment	Review article- expert opinion	Noticeable effect of ozone on virus and immune system
Rowen & Robins [29]	2020	USA	Predicting the position of ozone therapy for COVID-19	Review article- expert opinion	(1) Ozone -therapy as low-cost solution (2) Ozone oxides cysteine-rich virus
Valdenassi et al. [16]	2020	Italy	Demonstrate the potential effect of ozone on COVID-19	Review article- expert opinion	Ozone as immune modulator and improves oxygen circulation
Schwartz et al. [19]	2020	Spain	Investigate the potential effect of ozone therapy on COVID-19	Review- expert opinion	Guides to use ozone as COVID-19 treatment
Eren et al. [30]	2020	Turkey	Potential effect of ozone on SARS-COV-2	Review- expert opinion	Ozone reacts with thiol groups in COVID-19

Table 12.2 Characteristics of registered clinical trials

Registration no.	Title	Setting	Study design	Primary purpose	Recruitment status
ChiCTR2000030165	Clinical study for ozonated autohemotherapy for treatment of COVID-19	Tianjin, China	Non-randomized controlled trial	Chest CT Whole blood cell analysis Recovery rate Oxygenation index Inflammatory response index	Recruiting
ChiCTR2000030102	A multicenter randomized controlled trial for ozone autohemotherapy in the treatment of novel coronavirus pneumonia (COVID-19)	Tianjin, China	RCT (phase 0)	• Chest imaging • RNA test of COVID-19 • Time to remission / disappearance of primary symptoms • Completely antipyretic time • Incidence of medical complications during hospitalization • Blood oxygen saturation • Time to SARS-CoV-2 RT-PCR negativity	Recruiting
ChiCTR2000030006	A randomized controlled trial for the efficacy of ozonated autohemotherapy for treatment COVID-19	China, Wuhan	RCT	• Recovery rate	Recruiting

system. In addition, ozonides may suppress the cytokine storm. Ozone can also activate the cellular and humoral immune systems, increase proliferation of immunocompetent cells, and synthesize immunoglobulins, in addition to enhancing phagocytosis. It also stimulates signal transduction molecules via NRF2 and causes immune system improvement [23–25].

Ozone also stimulates aerobic metabolism as an anti-hypoxic agent. In addition, it activates protein synthesis and boosts cell metabolism. Ozone causes the synthesis of interleukins, leukotrienes, prostaglandins, and immunoglobulins which have an important biological role in the treatment process [26–28]. The main mechanisms behind ozone therapy are shown in Fig. 12.2 [28].

Focusing on coronaviruses, ozonized blood suppresses the cytokine storm in the body and improves the oxygen circulation [16, 19, 29]. Coronaviruses, including SARS-CoV-2, are rich in cysteine amino acid residues, which were essential for viral activity. It has been suggested that this property may make SARS-CoV-2 susceptible to ozone therapy because of the high oxidation capability of the ozone [29, 30]. Because of the capacity of ozone for full oxidation of substances such as the sulfhydryl groups of cysteine residues, ozone therapy could be an inexpensive and safe treatment of COVID-19 disease [29, 31].

3.4 Ozone Therapy and Viral Infections

The disinfectant effect of ozone on viruses as well as bacteria, spores, and fungus has been studied [32, 33]. Hudson et al. evaluated the

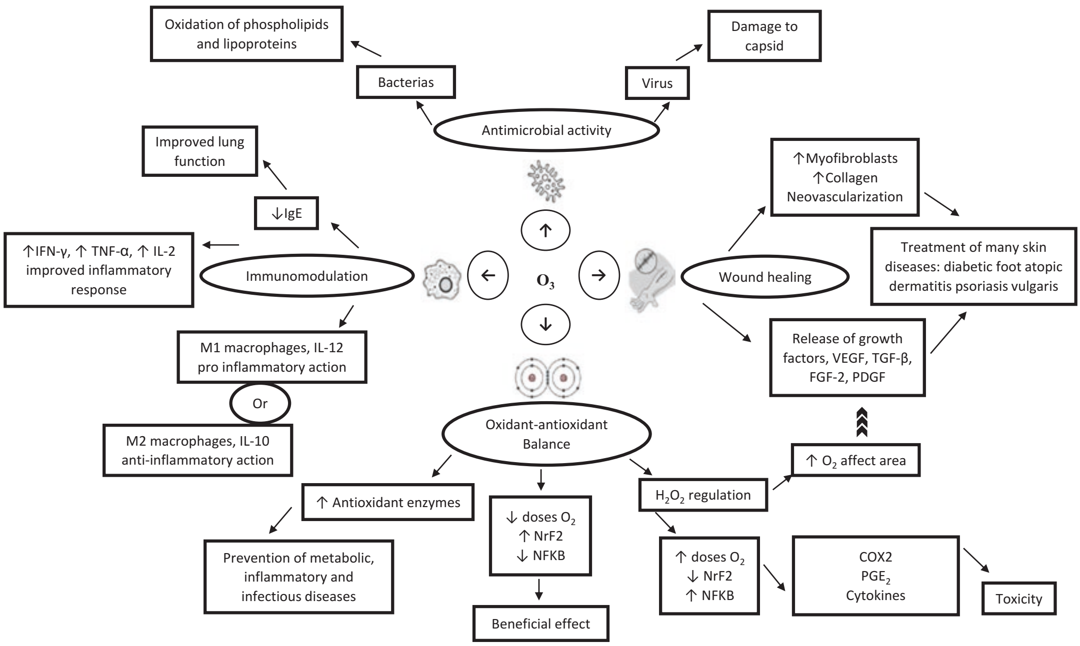

Fig. 12.2 The main mechanism behind ozone treatment (Pivotto et al. [28])

decontaminating effect of ozone on 12 different viruses via a mobile apparatus [34]. Influenza H3N2, herpes simplex virus type 1 (HSV), rhinovirus types 1A and 14, adenovirus types 3 and 11, sindbis virus (SINV), yellow fever virus (YFV), vesicular stomatitis virus (VSV), poliovirus (PV, vaccine strain), and vaccinia virus (VV) were tested on different surfaces and biological fluids. The results showed that inactivation occurred by factors of at least 1000-fold. Short periods of high humidity (>90% relative humidity) with peak ozone gas concentration (20–25 ppm) provided the optimum antiviral activity. Another study also confirmed that ozone exposure can similarly inactivate norovirus from surfaces, as confirmed by quantitative reverse transcriptase real-time polymerase chain reaction (RT-PCR) [35]. Maler and Chu studied the disinfectant efficacy of ozone in combination with ultraviolet treatment in of the polyoma virus [36]. Again, this revealed a significant reduction in the number of viruses and viable cells.

In addition to surface decontamination, some studies have evaluated the therapeutic effects of systemic ozone therapy for viral diseases. Ozone could affect both enveloped [herpes simplex virus type-1 strain McIntyre (HSV-1), vaccinia strain Elstree (VAC), vesicular stomatitis virus strain Indiana (VSV), influenza A strain (H1N1) A/WS/33], and non-enveloped [human adenovirus type 2 (Ad2)] viruses [16, 31]. In vitro studies examined ozone-treated serum for potential inactivation capability against HIV and the associated cytotoxic products [37]. This showed that ozone inactivated HIV-1 in a dose-dependent manner. The antiviral mechanisms observed included disruption of viral particles, reverse transcriptase inactivation, and disability to bind to receptors of target cells, all without apparent cytotoxicity [37, 38].

Rowen et al. administered combinations of ozone therapies to 5 patients with Ebola hemorrhagic fever [39]. In this study, direct intravenous ozone gas was infused at 55 μg/mL in 20–40 mL. Rectal ozone was also administered at a concentration of 36 μg/mL with a volume between 150 and 350 mL. Ozone water was made by bubbling ozone gas at approximately 70 μg/mL into the water, and this was taken orally for 15 min at a volume of 300–500 mL. All patients experienced full remission of symptoms within 2–4 days. Possible antiviral mechanisms included oxidation of sulfhydryl groups to disulfide which inactivated viral entry, attachment of the lipid envelope, oxidation of viral surface glycoproteins, and stimulation of the immune system. However, the effectiveness of ozone still requires confirmation in clinical trials.

3.5 Ozone Therapy and Respiratory System

Ozone cannot be inhaled directly because of its toxicity and irritancy via this route. However, it can be administered via the systemic circulation for lung diseases. Following are three clinical trials which studied the effect of ozone therapy on different respiratory diseases.

Asthma

Hernandez et al. recruited 113 asthmatic patients and divided them into three groups [14]. Two groups were treated by major ozone autohemotherapy (MAHT) for 3 cycles and 12 total sessions using an ozone dose of 4 mg (20 mg/mL per mL blood and 200 mL total volume) in the first group or 8 mg in the second group. The third group received ozone rectal insufflations (RIs) for 3 cycles over 20 sessions using an ozone dose of 10 mg (50 mg/mL and 200 mL total gas volume). Functional vital capacity (FVC) was increased significantly (2.34 vs. 2.99 L) in the 8 mg MAHT group while no significant changes were observed in the other groups. Improvement in symptoms such as dyspnea, wheezing, and medication was observed respectively in 8 mg MAHT, 10 mg RI, and 4 mg MAHT groups. The anti-inflammatory indicators IgE and HLA-DR were decreased, while increments in antioxidant agents of glutathione pathways were achieved with all treatments but more prominent in the 8 mg MAHT group. These findings indicated immunomodulatory and oxidative stress regulation effects of ozone therapy.

Chronic Obstructive Pulmonary Disease (COPD)

Fifty patients affected by moderate/severe COPD were enrolled in a clinical trial [40]. Half of the patients received major ozonated autohemotherapy, and the other half were entered as the control group. The protocol was as follows: 225 mL of blood was vacuumed from the antecubital vein into a sterile citrated glass bottle at a 9:1 ratio. Then 225 mL of 20 μg/mL ozone was added and mixed for 5 min and re-infused 15–20 min later. The only observed complication was facial redness in some of patients. Significant improvements were seen in the 6 min walking test, and dyspnea was observed in the ozone therapy group. However, there were no significant differences in resting arterial gas and pulmonary function tests.

Pulmonary Emphysema

Colunga et al. published a trial in Spanish studying the effect of ozone therapy on pulmonary emphysema and spirometry parameters [41]. Sixty-four patients were randomly assigned to treatment with either rectal ozone therapy, ozone therapy, or control (no treatment). At baseline, the intervention group had significantly lower values of forced expiratory volume in the first second (fEV1) and fEV1/forced vital capacity. However, at the end of the treatment period, these parameters were similar in the three groups with no difference in other spirometric parameters.

4 Discussion

This systematic review assessed the role and efficacy of ozone therapy as a potential treatment for COVID-19 disease, which shows dyspnea and respiratory distress as major features. Based on the extracted studies, it seems feasible that ozone therapy may be a suitable approach in the treatment of these aspects of COVID-disease [16, 19, 25, 29–31]. The studies showed that ozone therapy can be effective by 4 main routes: (1) virus inactivation; (2) modification of oxidative stress along with reduction of inflammation and apoptosis; (3) increased blood flow and tissue oxygenation; and (4) improvement of the immune response by stimulation of interferon gamma (IFN-γ) and pro-inflammatory cytokines [16, 19, 29, 31].

A number of studies in this review described a role of ozone therapy in infectious diseases. Ozone is known as a disinfectant and therapeutic substance in medicine [13]. In addition, some of the studies indicated the importance of ozone in the treatment of respiratory Illnesses such as COPD, lung fibrosis, pulmonary inflammation, and other lung diseases[14, 22]. The efficiency of ozone therapy in diabetic wounds, asthma, heart disease, cancer, and antibiotic-resistant diseases like methicillin-resistant Staphylococcus aureus (MRSA) and HIV has been demonstrated previously. The side effects of ozone include the probability of interference via the increased nitric oxide (NO) production subsequent to stimulation of antioxidant enzymes. In addition, ozone therapy may cause transmission disorder because NO can cause a further increase in NO levels [8, 22, 42]. However, there is not enough evidence supporting this possibility.

This review was limited by the lack of direct data concerning the effects of ozone therapy in COVID-19 disease.

5 Conclusions and Future Perspective

According to the evidence, it is postulated the ozone therapy is potentially effective in the treatment of COVID-19 disease. As no direct data were available, much of the information in this review has been extrapolated from of other viruses and respiratory conditions. Thus, there is still not sufficient evidence to endorse the efficacy of ozone therapy as a potential novel COVID-10 treatment. This will require at least partial completion of the ongoing clinical studies and establishment of further follow-up studies to address any gaps in the data.

Conflict of interest The authors declare no conflict of interest

References

1. Wu Z, McGoogan JM (2020) Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 323(13):1239–1242
2. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR (2020) Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and corona virus disease-2019 (COVID-19): the epidemic and the challenges. Int J Antimicrob Agents 55(3):105924. https://doi.org/10.1016/j.ijantimicag.2020.105924
3. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J et al (2020) China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 382(8):727–733
4. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y et al (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395(10223):497–506
5. Wang W, Tang J, Wei F (2020) Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. J Med Virol 92(4):441–447
6. Rothan HA, Byrareddy SN (2020) The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 109:102433. https://doi.org/10.1016/j.jaut.2020.102433
7. Choi H, Qi X, Yoon SH, Park SJ, Lee KH, Kim JY et al (2020) Extension of coronavirus disease 2019 (COVID-19) on chest CT and implications for chest radiograph interpretation. Radiol Cardiothorac Imaging 2(2):e200107. https://doi.org/10.1148/ryct.2020200107
8. Elvis A, Ekta J (2011) Ozone therapy: a clinical review. J Nat Sci Biol Med 2(1):66–70
9. Azarpazhooh A, Limeback H (2008) The application of ozone in dentistry: a systematic review of literature. J Dent 36(2):104–116
10. Viebahn-Hänsler R, Leon-Fernandez OS, Fahmy Z (2017) Systemic ozone applications, major autohemotherapy and rectal insufflation, evaluated according to the international classification of evidence-based medicine. A new basis for reimbursement of medical expenses by private and social insurances. J Ozone Ther 3(4):78. https://doi.org/10.7203/jo3t.3.4.2019.15550
11. Di Mauro R, Cantarella G, Bernardini R, Di Rosa M, Barbagallo I, Distefano A et al (2019) The biochemical and pharmacological properties of ozone: the smell of protection in acute and chronic diseases. Int J Mol Sci 20(3):634. https://doi.org/10.3390/ijms20030634
12. Clavo B, Santana-Rodríguez N, Llontop P, Gutiérrez D, Suárez G, López L et al (2018) Ozone therapy as adjuvant for cancer treatment: is further research warranted? Evid Based Complement Alternat Med 2018:7931849. https://doi.org/10.1155/2018/7931849
13. Allorto N (2019) Oxygen-ozone therapy: an extra weapon for the general practitioners and their patients. Ozone Ther 4(2). https://doi.org/10.4081/ozone.2019.8424
14. Hernández FR, Calunga JF, Turrent JF, Menéndez SC, Montenegro AP (2005) Ozone therapy effects on biomarkers and lung function in asthma. Arch Med Res 36(5):549–554

15. Denia JN. El Uso de ozonoterapia en salud. http://www.ozonoterapiaalbacete.com/ozonoterapia.html
16. Valdenassi L, Franzini M, Ricevuti G, Rinaldi L, Galoforo AC, Tirelli U (2020) Potential mechanisms by which the oxygen-ozone (O2-O3) therapy could contribute to the treatment against the coronavirus COVID-19. Eur Rev Med Pharmacol Sci 24(8):4059–4061
17. Centro Medico San Magno (2020) Secondo Report – Ossigeno Ozono Sioot Nei Pazienti Ricoverati Con COVID-19. www.ossigenoozono.it
18. Centro Medico San Magno (2020) Primo Report – Ossigeno Ozono Sioot Nei Pazienti Ricoverati Con COVID-19. www.ossigenoozono.it
19. Martínez-Sánchez ASG (2020) Potential use of ozone in SARS-CoV-2/COVID-19. https://aepromo.org/coronavirus/pdfs_doc_ISCO3/Covid19_en.pdf
20. Schwartz A, Sánchez GM (2012) Ozone therapy and its scientific foundations. Ozone Ther Glob J 2(1):199–232
21. Clavo B, Rodriguez-Esparragon F, Rodriguez-Abreu D, Martinez-Sanchez G, Llontop P, Aguiar-Bujanda D et al (2019) Modulation of oxidative stress by ozone therapy in the prevention and treatment of chemotherapy-induced toxicity: review and prospects. Antioxidants (Basel) 8(12):588. https://doi.org/10.3390/antiox8120588
22. Bocci V (2007) The case for oxygen-ozonetherapy. Br J Biomed Sci 64(1):44–49
23. Jaramillo F, Vendruscolo C, Fülber J, Seidel S, Barbosa A, Baccarin R (2020) Effects of transrectal medicinal ozone in horses-clinical and laboratory aspects. Arq Bras Med Vet Zootec 72(1):56–64
24. Seidler V, Linetskiy I, Hubálková H, Stankova H, Smucler R, Mazánek J (2008) Ozone and its usage in general medicine and dentistry. A review article. Prague Med Rep 109(1):5–13
25. Ricevuti G, Franzini M, Valdenassi L (2020) Oxygen-ozone immunoceutical therapy in COVID-19 outbreak: facts and figures. Ozone Ther 5(1). https://doi.org/10.4081/ozone.2020.9014
26. Erden G, Demir O, Filibeli A (2010) Disintegration of biological sludge: effect of ozone oxidation and ultrasonic treatment on aerobic digestibility. Bioresour Technol 101(21):8093–8098
27. Saini R (2011) Ozone therapy in dentistry: a strategic review. J Nat Sci Biol Med 2(2):151–153
28. Pivotto AP, Banhuk FW, Staffen IV, Daga MA, Ayala TS, Menolli RA (2020) Clinical uses and molecular aspects of ozone therapy: a review. Online J Biol Sci 20(1):31–49. https://doi.org/10.3844/ojbsci.2020.37.49
29. Rowen R, Robins H (2020) A plausible "penny" costing effective treatment for Corona virus ozone therapy. J Infect Dis Epidemiol 6:113. https://doi.org/10.23937/2474-3658/1510113
30. Eren E, Saribek F, Kalayci Z, Yilmaz N (2020) How to cripple SARS-COV-2 virus with ozone treatment Thiol groups in viruses and SARS-COV-2. £rd WorldConference on Traditional and Complementary Medicine. Scheduled December 10–11 in Dubai, UAE (now Webinar due to COVID-19 restrictions). https://vircos.it/wp-content/uploads/2020/06/HowtocrippleSARSpresentation.pdf
31. Galoforo AC, Scassellati C, Bonvicini C (2020) Coronavirus: Dall' Ozono una possibile soluzione? Il Popolo Veneto; Mar 5. https://www.ilpopoloveneto.it/notizie/lifestyle/salutebenessere/2020/03/05/97494-coronavirus-dallozono-una-possibile-soluzione
32. Ding W, Jin W, Cao S, Zhou X, Wang C, Jiang Q et al (2019) Ozone disinfection of chlorine-resistant bacteria in drinking water. Water Res 160:339–349
33. Sankaran S, Khanal SK, Pometto IIIAL, van Leeuwen JH (2008) Ozone as a selective disinfectant for nonaseptic fungal cultivation on corn-processing wastewater. Bioresour Technol 99(17):8265–8272
34. Hudson JB, Sharma M, Vimalanathan S (2009) Development of a practical method for using ozone gas as a virus decontaminating agent. Ozone Sci Eng 31(3):216–223
35. Hudson J, Sharma M, Petric M (2007) Inactivation of norovirus by ozone gas in conditions relevant to healthcare. J Hosp Infect 66(1):40–45
36. Maier I, Chu T (2016) Use of ozone for inactivation of bacteria and viruses in cryostats. J Cytol Histol 7(428):2. https://doi.org/10.4172/2157-7099.1000428
37. Wells KH, Latino J, Gavalchin J, Poiesz BJ (1991) Inactivation of human immunodeficiency virus type 1 by ozone in vitro. Blood 78(7):1882–1890
38. Carpendale MT, Freeberg JK (1991) Ozone inactivates HIV at noncytotoxic concentrations. Antivir Res 16(3):281–292
39. Rowen RJ, Robins H, Carew K, Kamara MM, Jalloh MI (2016) Rapid resolution of hemorrhagic fever (Ebola) in Sierra Leone with ozone therapy. Afr J Infect Dis 10(1):49–54
40. Borrelli E, Bocci V (2014) Oxygen ozone therapy in the treatment of chronic obstructive pulmonary disease: an integrative approach. Am J Clin Exp Med 2(2):29–13
41. Calunga J, Paz Y, Menéndez S, Martínez A, Hernández A (2011) Rectal ozone therapy for patients with pulmonary emphysema. Rev Med Chil 139(4):439–447
42. Smith NL, Wilson AL, Gandhi J, Vatsia S, Khan SA (2017) Ozone therapy: an overview of pharmacodynamics, current research, and clinical utility. Med Gas Res 7(3):212–219