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Nasal Inhaled Formulation for COVID-19: An Article

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ABSTRACT

The coronavirus-2 (SARS-CoV-2) that causes Coronavirus Disease-2019 (COVID-19) has sparked a global epidemic. COVID-19 had afflicted 178 million individuals globally as of June 22, 2021, with 3.87 million people dying as a result. According to the Centers for Disease Control and Prevention (CDC), of the United States, the COVID-19 virus is mostly spread between humans, through droplets in the lungs and contact pathways. Since the initial infection and sickness occurs in this location, the lungs are the primary route of advancement, with medicines delivered directly to the lungs via inhalation. For COVID-19 treatment, this may be the best route of administration. The goal of this review is to highlight potential COVID-19 inhalation treatments. The comparison of SARS-CoV-2 is discussed in this review.

COVID INFORMATION[2-5]: Coronavirus disease (COVID-19) is a novel virus that causes an infectious disease. The majority of patients infected with the COVID-19 virus will have mild to moderate respiratory symptoms and will recover without needing any specific therapy. The best way to prevent and slow down transmission is to be well informed about the COVID-19 virus, the disease it causes, and how it spreads. Protect yourself and others from infection by washing your hands or using an alcohol-based rub frequently and not touching your face. When an infected individual coughs or sneezes, the COVID-19 virus transmits predominantly through droplets of saliva or discharge from the nose, therefore respiratory etiquette is particularly vital (for example, by coughing into a flexed elbow).

CORONA VIRUS LIFE CYCLE[6,7]: Viral Structure and Mechanism

Coronaviruses, including SARS-CoV-2, are enclosed positive-sense RNA viruses with a genome length of about 30,000 nucleotides that encode 16 nonstructural proteins and at least four primary structural proteins, but the exact number varies across Coronavirinae members (Figure No. 1). [7] Coronavirus particles are spherical, with an average diameter of 125 nm, and the progeny are derived from them. responsible for the name of the genus. Coronavirus particles also contain the E and M integral membrane proteins, a host-derived lipid envelope, and a helical viral nucleocapsid containing the N protein and viral genomic RNA, in addition to the spike glycoproteins.

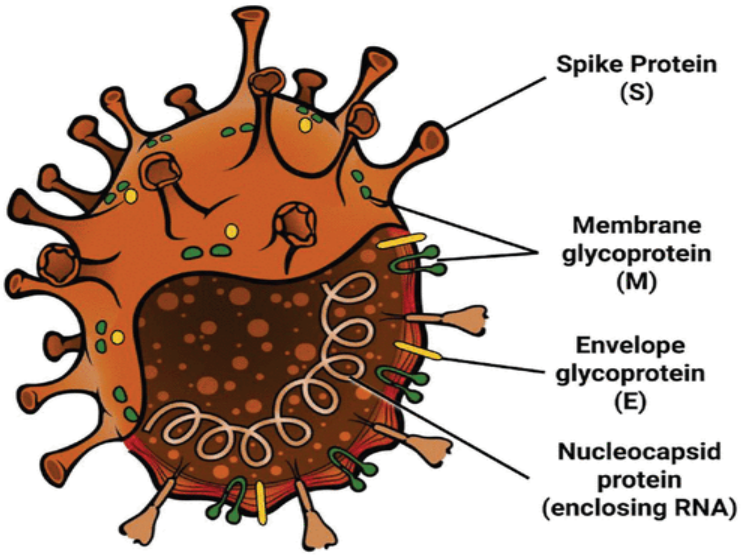

Figure No. 1: Structure of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

As summarized in Figure No. 2 the attachment of the viral particle to the host cell via the viral spike glycoprotein starts the coronavirus cellular viral life cycle. The human angiotensin-converting enzyme 2 protein is used by the SARS-CoV-2 virus, as well as the original SARS virus (SARS-CoV-1) and the endemic human coronavirus HCoV-NL63. 9A sequence of two proteolytic cleavage events of the spike glycoprotein is required for virus entry into the host cytoplasm, revealing the fusion peptide, which facilitates the fusion of the viral and cellular lipid bilayers. The viral replicase complex, which is made up of 16 nonstructural proteins encoded by the genomic RNA, is expressed when the viral RNA is delivered into the cytoplasm. Viral RNA synthesis produces a nested set of mRNA transcripts within the viral replication compartment using a complicated discontinuous RNA synthesis mechanism that generates complementary negative-sense RNA templates. The remaining viral structural proteins are created by nested mRNAs, and progeny viral genomes are produced by continuous viral RNA synthesis. Infected cells' cytoplasm produces new viral nucleocapsids, and mature viral particles are budded into the ERGIC (endoplasmic reticulum–Golgi intermediate complex) via contact between the ERGIC membrane-associated M protein and the nucleocapsid's N protein. Smooth-walled vesicles transport the mature virus particles to the cell membrane, where they are released into the extracellular environment.

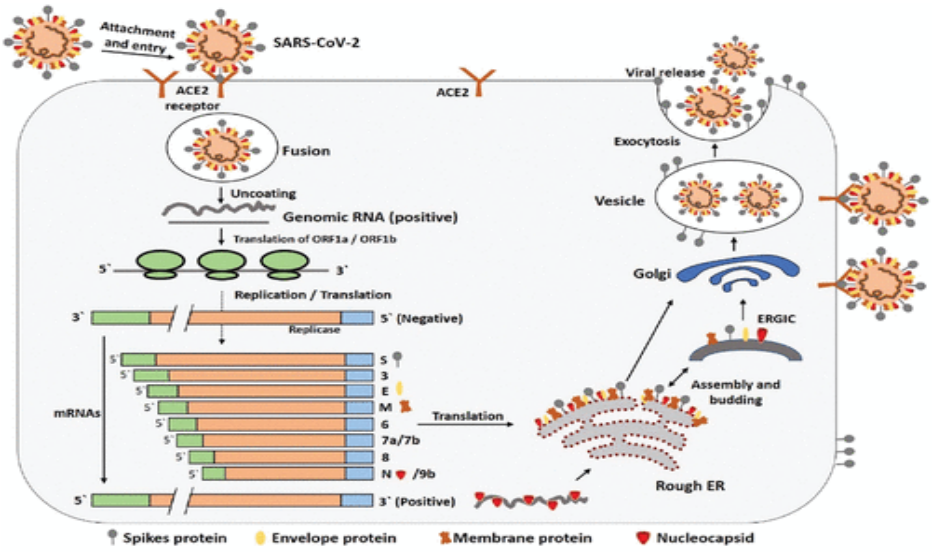

Figure No. 2: The life cycle of SARS-CoV-2 in host cells.

ACE2, angiotensin-converting enzyme 2; ER, endoplasmic reticulum; ERGIC, ER–Golgi intermediate compartment. Reprinted from Shereen et al. (2020).

To date, seven coronaviruses capable of infecting humans have been discovered, accounting for 5% to 10% of all acute respiratory infections. The majority of endemic coronaviruses induce self-limiting upper respiratory infections, although SARS-CoV, SARS-CoV-2, and the Middle Eastern respiratory syndrome coronavirus (MERS-CoV) have significantly high fatality rates. SARS-CoV-2 appears to be transmitted primarily through respiratory droplets6, with secondary surface contact and aerosol transmission also being possibilities. In most cases, the incubation period is 3 to 7 days, with a delay of up to 2 weeks between infection and onset of symptoms. The significant basic reproduction number (R0) of 2.5 to 3.10 is assumed to be due to this protracted asymptomatic phase. Viral shedding has been seen in the nasal cavities, nasopharynx, sputum, oropharynx, bronchial fluid, and stool, among other places.[11] The oropharynx, on the other hand, had a substantially greater detection rate. 12

Figure No. 3:

NASAL INFORMATION (1, 9-12): To find relevant peer-reviewed English literature about intranasal use of medicines and agents having antiviral capabilities, a search of PubMed, Embase, and Clinicaltrials.gov was done. To examine and synthesize the literature, a multidisciplinary team of experts in otolaryngology, infectious diseases, public health, pharmacy, and virology was convened. In the context of the COVID-19 pandemic, a series of video conferences were convened to analyze the findings and discuss prospective applications of intranasal antiviral medicines. The panel covered several issues that should be

considered while using intranasal antiviral drugs. (Figure No. 4). Agents were tested for antiviral activity against SARS-CoV-2 and other viruses, as well as efficacy and feasibility in human intranasal use. Mucosal or skin irritation, odour and taste disturbances, headaches, allergic reactions, nose hemorrhage, fungal infection or colonization, and rhinosinusitis were all investigated as potential intranasal side effects. Adequacy of target or viral cell infiltration methods, routes of distribution, medium suspension, additions to increase mucosal or cellular absorption of the agents, and the dependability of synthesizing these compounds were also discussed.

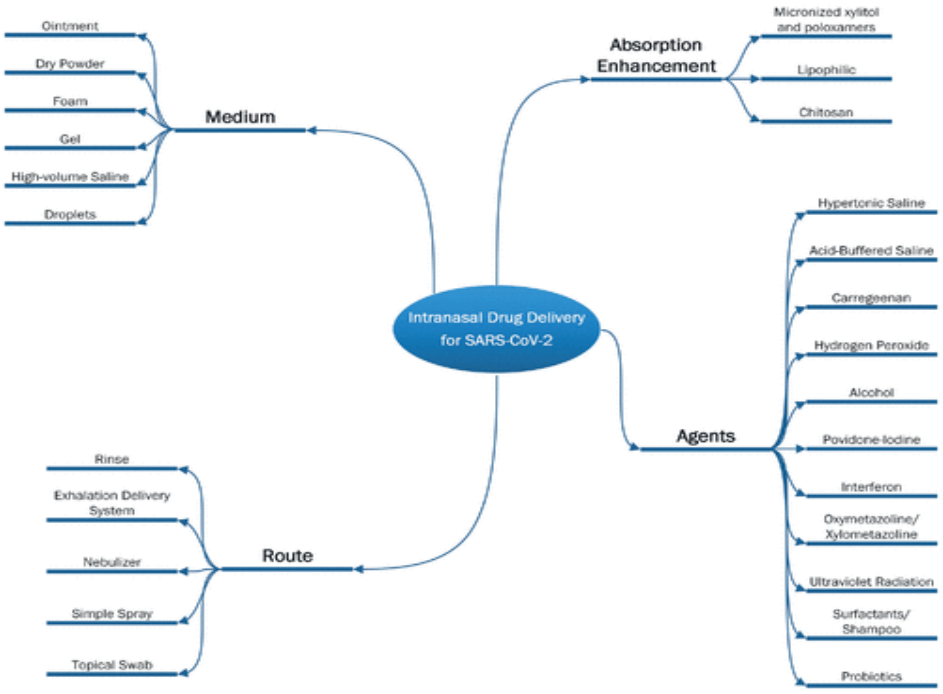

Figure No. 4: Mind map displaying the ideas and concepts of intranasal drug delivery in the setting of antiviral disease, including SARS-CoV-2.

The central topic has branches extending radially to connect subtopics. Each subtopic is connected to key concepts.

Route and Medium of Drug Delivery [13, 14, 16]

[A]Solution Sprays*:* Intranasal medication delivery has been intensively studied and used for allergic rhinitis, chronic rhinosinusitis, opioid overdose, and topical anesthesia/decongestion for many years. The relative ease of usage in a home context and good patient tolerance are two factors that make this delivery option appealing. Because these sprays are aerosolized and potentially cause sneezing or coughing, the risk of viral shedding is uncertain. Most nasal

sprays produce an aerosol that settles in the front of the nose, with mucociliary clearance transporting drugs deeper into the nasal cavity. Newer nasal sprays for exhalation delivery have been demonstrated to spread further within the nasal cavity. (Figure No. 5). Nasal nebulizers have also been used to treat chronic rhinosinusitis and nasal polyposis; however, the medicine distribution is similar to that of exhalation delivery systems, and the related equipment cost is higher. Because the mucous layer in the nose regenerates every 20 minutes and is dumped into the nasopharynx, the speed with which the medication dissolves and penetrates the mucosa is crucial for drug efficacy. Computational fluid dynamics could be used to help guide effective therapy by determining optimum particle size, spray velocity, and dose.

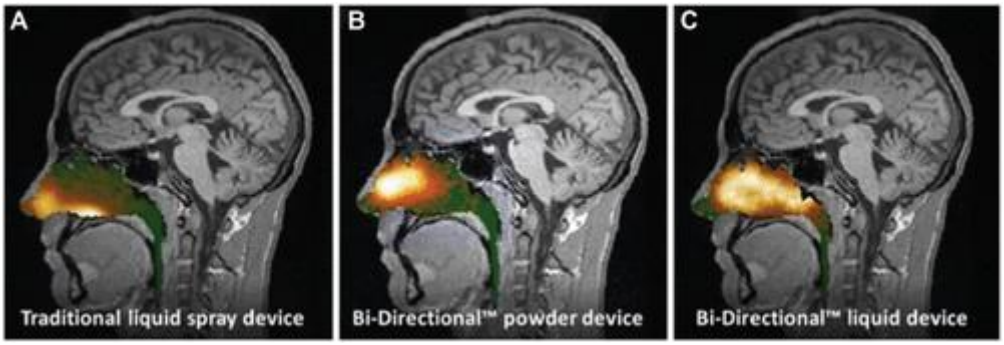

Figure No. 5: Gamma camera image data from the nasal cavity superimposed on the corresponding sagittal MRI section showing deposition two minutes after delivery using (A) a traditional liquid spray, (B) a breath-powered powder device, and (C) a breath-powered liquid spray device incorporating the same spray pump. Djupesland et al. are reprinted (2012).

[B]Saline Rinses: Intranasal saline rinses, like solution sprays, are readily accessible, can be used with or without pharmaceuticals, and are generally well tolerated. More research into the risk of viral shedding is required. The removal of the mucous barrier with the rinse action is said to provide the best interface between the medicine and the mucosa itself, compared to sprays. 82 To be administered in this manner, however, pharmaceutical compositions must be water-soluble.

[C]Gel: Alzheimer's illness, migraines, depression, and schizophrenia have all been treated with intranasal nanogels. 83 This medium can be used for both hydrophilic and hydrophobic medicines, unlike the aforementioned intranasal sprays and rinses, which require a suspension. Additionally, the gel formulation's higher viscosity may extend the drug's

residence duration on the nasal mucosa, resulting in increased drug absorption through the mucosa. 84 Increasing viscosity may interfere with regular ciliary beating, resulting in unfavorable side effects. Keeping stable formulations with regular dosing while maintaining appropriate shelf life, as well as creating an efficient delivery mechanism to distribute the gel within the nasal cavity, are also challenges. Wang et al. 85 presented a hybrid of technologies using in situ gel-forming methods, in which a solution instilled intranasally transitions to a viscoelastic gel. Increased nasal cavity retention and mucous membrane permeability are two advantages of this approach.

[D]Foam/Packing: For many years, otolaryngologists have used intranasal foam and dissolvable packing to treat epistaxis, chronic rhinosinusitis, and postsurgical sinus cavities. Drug delivery applications for psychiatric illnesses like bipolar disorder and schizophrenia have also been investigated. Chitosan, carboxymethylcellulose, hyaluronic acid, and synthetic polyurethane foam are examples of intranasal foams. Nanoparticles that act as reservoirs for hydrophobic medicines can be mixed into these foams to improve mucoadhesive characteristics and medication absorption. Most otolaryngologists use direct administration by a medical practitioner rather than patients themselves, therefore this method would be more difficult for individuals to self-administer. Furthermore, because these foams are typically given with at least a topical anesthetic, they may be less well accepted, causing more sneezing and discomfort than sprays or rinses.

[E]Dry Powders: Dissolve the drug in a hydrofluoroalkane propellant, which has just been released. Propylene glycol, isopropyl alcohol, and PEG400 are nonaqueous propellants that have been reported to produce local irritation with long-term use; consequently, careful consideration of propellant selection and associated adverse effects is required. Other difficulties with powder use include distributing within the nasal cavity, controlling particle size, protecting the powder's viability from humidity. Although most intranasal sprays on the market are liquid solutions, recreational drugs have long been used in powder form. Dry mist nasal sprays, which during storage, and maximizing absorption by the mucous membranes.

[F] Ointment: Nasal ointments have long been used to treat folliculitis in the nasal vestibule and to avoid epistaxis; nevertheless, interest in drug delivery via nasal ointments, such as for allergic rhinitis, has grown recently. Patients can simply apply these ointments to the anterior nasal vestibule using intranasal swabs, with mucociliary clearance transporting drugs deeper into the nasal cavity. Higher-viscosity ointments have a lesser potential to spread and may

lengthen the duration they remain in the nasal cavity. The ointment's lipophilic characteristics may help it absorb better through the nasal mucosa. Long-term nocturnal intranasal application of ointments, notably long-chain mineral hydrocarbons, has been linked to paraffin granulomas and case reports of lipoid pneumonia.

DRUG USE IN NASAL FORMULATION[19-25]: Agents With Antiviral Capability

While no medicine has been produced to specifically treat the SARS-CoV-2 virus, ultraviolet (UV) radiation, heat, ether, ethanol, and isopropanol have all been proven to inactivate SARS-CoV-2 on surfaces. Other viruses have been used to study other agents.

- **Alcohol and Isopropanol**

The World Health Organization (WHO) recommends two alcohol-based formulations for hand cleanliness in health care: ethanol and isopropanol. These chemicals are fast-acting, low-cost, and broad-spectrum, with the ability to inactivate SARS-CoV and MERS-CoV in the past. Hand sanitizer formulas should include at least 60 % ethanol or 70 % isopropanol, according to the WHO. Both alcohols, however, have been shown to inactivate the SARS-CoV-2 virus down to a concentration of 30a certain percentage A placebo-controlled randomized controlled study (RCT) comprising 387 health care employees looked explored the intranasal application of alcohol formulations. Swabs of 70 percent ethanol coupled with natural oil emollients and the preservative benzalkonium chloride or placebo were swabbed intranasally three times a day on health care workers colonized with nasal Staphylococcus aureus. When compared to placebo, antiseptic usage reduced S aureus colony-forming units by a median of 99 percent (P.001). During the trial, no adverse effects were reported by the subjects.

- **Povidone-Iodine**

Povidone-iodine (PI) kills bacteria and viruses quickly, including SARS-CoV and MERS-CoV. It has been used as a skin disinfectant, as well as an oral wash or gargle rinse, in therapeutic settings. 3M created and tested an intranasal formulation applied to the anterior nares (PI solution, 5% wt/wt [0.5 percent accessible iodine]; United States Pharmacopeia). The Draize scale revealed no substantial discomfort when a blinded expert grader assessed the level of intranasal skin erythema and edema in 30 individuals. Intranasally, formulations of 5 % to 10 % PI were tested for potential adverse effects, and the results showed no gross

harm, albeit ciliotoxicity has been demonstrated *in-vitro* at these dosages. In a randomized controlled trial, nasal administration of 10 % PI, 5 % PI, or placebo before arthroscopic surgery for methicillin-resistant *S. aureus* prophylaxis resulted in identical rates of nasal irritation. A study of PI's free iodine concentration *in-vitro* revealed a link between free iodine concentration and virucidal efficacy. However, ciliotoxicity was observed in a research of 5 % and 10 % PI applied to ciliated human pulmonary epithelial cells. Lower-concentration formulations (0.5 percent PI [Nasodine]) were shown to have no cytotoxicity or ciliotoxicity when applied *in-vitro* to air-liquid interface cultures of primary human nasal epithelial cells. Patients and health care personnel working in head and neck oncologic treatment who are at risk of COVID-19 exposure have been urged to consider taking PI intranasally or orally as a prophylactic measure. Following surgery with oral PI, aspiration pneumonitis has been documented, as well as discoloration of the teeth and tongue.

- **Carrageenan**

Carrageenan is a polymer derived from red seaweed that is commonly used as a food thickener. Carrageenan has antiviral effects against human rhinovirus and influenza A *in-vitro* and in animals, preventing viral attachment to host cells without systemic absorption or nasal mucosal penetration. Four randomized controlled trials (RCTs) compared iota-carrageenan nasal spray to placebo saline spray in the treatment of respiratory viral infections (including rhinovirus, enteroviruses, and influenza) with varying reductions in symptoms and viral loads. Carrageenan-containing nasal sprays are available over the counter, however, the Food and Drug Administration (FDA) has only approved it as a food additive for human consumption at this time.

- **Acid-Buffered Saline**

For virus inactivation, an acidic pH is usually utilized. In the pharmaceutical sector, acidic solutions are often used to inactivate viruses, isolate viral proteins, and clean and prevent infection. Inactivation of influenza A, decreased symptoms and viral shedding of influenza A, reduced viral shedding of human rhinovirus with the use of solutions and nasal gels, and reduced symptom severity and duration of illness in the common cold have all been demonstrated using acid-buffered saline as a topical therapy for various upper respiratory viruses, unfortunately, SARS-CoV-2 has been demonstrated to be highly stable in a variety of pH settings, making acidic therapy ineffective against this virus.

- **Hypertonic Saline**

It may help to alleviate symptoms caused by a variety of upper respiratory viruses, as well as minimize viral shedding and promote inactivation. *In-vitro* research by Ramalingam et al. showed that increasing the availability of NaCl can help non-myeloid cells' innate immune response by boosting intracellular hypochlorous acid levels. Ramalingam et al. reported that using hypertonic saline irrigation and gargling for the common cold reduced symptom intensity, length of illness, intrahousehold transmission, and viral shedding in an RCT. With some complaints of nose discomfort, headache, and epistaxis, meta-analyses have demonstrated good tolerability.

- **Hydrogen Peroxide**

H_2O_2 has long been recognized to promote viral inactivation, and 0.5 percent H_2O_2 effectively deactivates SARS-CoV-2 on surfaces. 40,41 While H_2O_2 is routinely used for surface, surgical, and oral disinfection 40, there are currently no human clinical trials demonstrating the safety or usefulness of H_2O_2 intranasally.

- **Probiotics**

The use of ingested oral probiotics has been studied in the current COVID-19 pandemic, but the evidence is based on small case studies and correspondences, and experts concluded that even if oral probiotics were effective, they were unlikely to have a direct effect on the severe acute respiratory syndrome that most COVID-19 patients experience. The nasal and gastrointestinal microbiomes, on the other hand, appear to play an essential role in the innate immune system, notably in the defense against respiratory viral infections. In rhinovirus, nasal microbiota clusters were linked to the host's inflammatory response, viral load, and symptom severity despite the addition of oral probiotics having no significant effect on the host microbiome, the Corynebacterium-rich cluster of patients had overall lower symptoms during rhinovirus infection (nasal and gastrointestinal). In an *in-vivo* mouse model, *Corynebacterium* was also demonstrated to be protective against respiratory syncytial virus infection. In a mouse model, Zelaya et al. discovered that introducing *Lactobacillus* through the nose helped reduce influenza-related lung damage and inflammation. While the effects of orally delivered probiotics on several viruses have been investigated, we identified no research specifically looking into the use of intranasal probiotics to treat human upper

respiratory virus infections. For COVID-19 and other upper respiratory viral infections, more research into probiotic nasal and oral administration is needed.

- **Surfactants/Shampoo**

Surfactants, especially infant shampoo, have been widely researched in chronic rhinosinusitis. The majority of investigations have looked at bactericidal and antibiofilm effects. There were no studies that looked at the use of surfactant in the nasal cavity and its capacity to prevent or reduce viral infection. Intrinsic pulmonary surfactant, on the other hand, has been discovered to be a crucial component of our innate immune system, and its use has recently been demonstrated to aid in the prevention of various respiratory viruses, including H1N1 and influenza. The phospholipids in pulmonary surfactants are hypothesized to protect against viral infections by preventing viral binding to epithelial cells. Surfactants could be used to produce similar results in the upper aerodigestive tract, but this has yet to be investigated. The effect of saline irrigations and baby shampoo/saline irrigations on COVID-19 patients is the subject of one proposed trial. The tolerance of most surfactants has been reported to be satisfactory, although a surfactant ingredient in nasal saline rinses has been linked to nasal congestion and transitory scent loss in healthy participants.

- **UV Radiation**

UV radiation is classified as UV-C (100-280 nm), UV-B (280-320 nm), and UV-A (320-320 nm) based on their biological effects (320-400 nm). The majority of data regarding UV light's biological effects has come from dermatology, where several types of phototherapy have been used for decades. Other rhinologic disorders have been investigated with intranasal phototherapy, owing to its immunomodulating influence on inflammatory processes. Two randomized controlled trials found that a combination of low-dose UV-B, low-dose UV-A, and visible light helps to decrease symptom scores of ragweed-induced allergic rhinitis that is controllable by antiallergic medications. However, a similar treatment protocol does not appear to have efficacy for treatment effective for chronic rhinosinusitis. At the exposure levels used in the studies cited, the carcinogenic risk of rhinophototherapy on the nasal mucosa appears below. Patients with allergic rhinitis who receive intranasal phototherapy have nasal epithelial cells that can repair UV-induced DNA damage. Significant DNA damage was found immediately following the conclusion of the two-week therapy, which was reduced at the 10-day evaluation but was comparable to the control group at the two-

month follow-up. Human skin *in-vitro* and animal models showed similar repair kinetics in parallel experiments. At lower dosages, animal trials with UV-A and UV-B irradiation show no histopathologic alterations or induction of apoptosis. Other animal investigations have found that phototherapy reduces histopathologic alterations in the same way that nasal corticosteroid treatment does without increasing mucosal cell death.

UV-C is the most damaging wavelength range for bacteria because it is strongly absorbed by their nucleic acids. UV-C sterilization has been presented as an effective approach for disinfecting the water supply and saline irrigation bottle at the same time, and it has been used in tandem to lower SARS-CoV-2 titers in human blood transfusions to undetectable levels. UV exposure of the wound during surgery has been shown in multiple clinical investigations dating back to the 1940s to significantly reduce surgical site infection rates. Traditional UV-C light sources, which typically emit at 254 nm, are, on the other hand, a human health threat, causing skin cancer and cataracts. Far-UV-C light in the range of 207 to 222 nm, on the other hand, has the same bactericidal potential as 254-nm light but does not harm mammalian cells and tissues. Far-UV-C light does not penetrate the outer layer of the skin or the outer surface of the eyes due to its short range in biological materials, but it can effectively inactivate the nucleic acids and proliferative potential of surface bacteria. While UV-A and UV-B light delivered through the nose is safe, phototherapy at this wavelength has poor antibacterial action. Although UV-C radiation is a good disinfection procedure, no research has been done on the intranasal safety profile of UV-C phototherapy.

- **Oxymetazoline and Xylometazoline**

Nasal decongestants such as oxymetazoline and xylometazoline are routinely used over-the-counter. Local irritation and rhinitis medicamentosa, in which usage causes a paradoxical nasal blockage, are among the side effects. In small investigations, topical oxymetazoline nasal spray reduced rhinovirus viral load temporarily. 68 Other viruses, including SARS-CoV-2, have not been examined with these drugs. Given that they have been demonstrated to lower rhinovirus viral load, using them before nasal swab viral testing may be prudent.

- **Interferon[1, 4]**

Interferons are complex cytokines that play an important role in innate cellular immunity. They get their name from their capacity to prevent viral multiplication. Interferons boost the expression of MHC molecules (major histocompatibility complex). Viral presentation to

cytotoxic T lymphocytes is upregulated when MHC I expression is increased. MHC II stimulation enhances the helper T-cell response and the subsequent production of cytokines that boost the activity of other immune cells. Type 1 interferons, which release fibroblasts and monocytes with interferon-specific receptors, were activated by viral cellular invasion. As a result, the JAK-STAT signaling pathway (Janus kinase–signal transducer and activator of transcription) is activated. The production of proteins that hinder viral replication follows as a side effect. Interferon's role in SARS-CoV-2 is intriguing yet ambiguous. The SARS-CoV-2 virus enters the cell after a spike protein domain binds to the ACE2 receptor, which is increased by interferons and thought to assist lung cells to survive damage. Viral cellular invasion stimulated Type 1 interferons, which release fibroblasts and monocytes with interferon-specific receptors. As a result, the JAK-STAT (Janus kinase–signal transducer and activator of transcription) signaling pathway is activated. As a side effect, proteins that inhibit viral replication are produced. The role of interferon in SARS-CoV-2 is intriguing but unclear. After a spike protein domain attaches to the ACE2 receptor, which is boosted by interferons and thought to help lung cells withstand damage, the SARS-CoV-2 virus penetrates the cell. Others believe Type 3 interferons, particularly interferon lambda, could be a better treatment option for respiratory infections. Interferon lambda was found to be superior to Type 1 interferons in the respiratory tract due to its specificity, which reduced systemic adverse effects - specifically, an inflammatory response that Type 1 interferons can cause. In viral-mediated respiratory illness, aerosolized interferon treatment is efficacious. Fatigue, headache, pyrexia, myalgia, rigors, and mental problems have all been linked to Type 1 interferons. The proprietary interferon beta-1a formulation is the only aqueous preparation and is pH balanced to the respiratory mucosa, making it an ideal therapeutic for inhalation. Although this study failed to meet its primary endpoint of better asthma control, it did show good evidence of enhanced innate immunity with increased production of antiviral genes in induced sputum.

Topical interferon appears to be a promising target for SARS-CoV-2 treatment. The medicine was used as a preventative for health care workers in Hubei, China, and preliminary results show that none of the 2944 health care professionals who used it as a nasal drop contracted any infections. While more research into well-conducted prospective studies is needed in the peer-reviewed literature, this medication has a lot of potential as a well-tolerated, easy-to-deliver topical preventive against SARS-CoV-2 infection.

Enhancing Mucosal Absorption Efficiency[18, 22, 24]: Enhanced absorption rate, possibly increased bioavailability due to avoidance of hepatic first-pass metabolism, and a less acidic pH environment is all advantages of nasal mucosa as a drug delivery medium. Poor membrane retention duration, a restricted absorption value, breakdown via mucolytic enzymes, and constant mucociliary movement leading to washout are all problems.

- **Chitosan**

Chitosan is a cationic polysaccharide that has been explored extensively for its mucoadhesive-enhancing effects in the delivery of medications. Chitosan can have a variety of chemically altered functional groups to improve mucoadhesive properties and permeation effects by opening epithelial tight junctions, and several studies have shown that chitosan-bound medications are superior to unbound medications in terms of mucoadhesive properties and permeation effects. Chitosan is now approved by the FDA for use as a wound-healing agent. However, research on nasal chitosan-based antiviral medicines has been restricted. More research into prospective nasal chitosan-based antiviral medicines is needed, given chitosan's versatility and studies as a powerful mucoadhesive with relatively minimal toxicity.

- **Liposomes**

Drug transport through lipid bilayer cell membranes has been enhanced by lipophilic/liposomal formulations. Liposomal drug formulations are used in many FDA-approved drugs, including doxorubicin, amphotericin B, and others. Liposomal formulations have been reported to boost drug bioavailability across the mucosal membrane barrier in several *in-vitro* and *in-vivo* animal experiments. Despite a large amount of research into chitosan and liposomal nasal nanoparticle formulations, there are currently no FDA-approved chitosan- and liposomal-based nasal medication delivery systems, and more human research is needed to demonstrate clinical safety and efficacy.

- **Poloxamers**

Poloxamers are a type of nonionic copolymer with amphiphilic and surface-active characteristics that are water-soluble. A sol-to-gel transition occurs when the temperature of their aqueous solutions rises above a threshold gelation temperature. Hydrogels are used to help a medicine release locally and sustainably, reducing drug dosage, decreasing

administration frequency, and preventing side effects. Poloxamers have been approved by the FDA as a nontoxic solubilizer, emulsifier, and stabilizer that can be used orally, parenterally, or topically.

COVID INHALED DRUG: COVID-19 Therapeutics inhaled[1, 3 - 7, 49]

For the treatment of lung illnesses and diseases, inhaled medicines are increasingly widely used and highly recommended. Inhaled zanamivir for influenza and inhalation ribavirin for respiratory syncytial virus infections are among the several FDA-approved inhaled medicines for respiratory illnesses on the market. Lung pneumonia and other acute respiratory tract problems are common in SARSCOV-2 patients; as a result, a variety of medications have been developed to effectively treat lung pneumonia, including steroidal, antibacterial, and antiviral treatments. Below are examples mentioned in the literature for inhaled medications to treat different lungs complications.

Table No. 1:

Drug	**Category**	**Chemical Nature**	**Mode of Action**	**Inhaled Dose and Formulation/Device**
Remdesivir	Antiviral	Nucleoside analogue	RNA polymerase inhibitor	31 mg and 62 mg (nebulizer)
Ciclesonide	Anti-inflammatory	Corticosteroid	Anti-inflammatory action	800 µg/day (MDI, Alvesco)
Budesonide	Anti-inflammatory	Corticosteroid	Anti-inflammatory action	800 µg twice daily for 14 days (DPI, Pulmicort Turbohaler)
Furosemide	Loop diuretic	Chlorobenzoic acid	Sodium-potassium-2 chloride	40 mg (nebulizer)

Drug	Category	Chemical Nature	Mode of Action	Inhaled Dose and Formulation/Device
			(Na+-K+-2 Cl−) cotransporter inhibitor	
Nitric Oxide	Pulmonary vasodilator	Oxides of nitrogen	Increases intracellular cGMP	250 µg/kg IBW/h (INOpulse®)
Epoprostenol	Pulmonary vasodilator	Prostaglandins I	Increases intracellular cAMP levels and antagonist of thromboxane A2	VentaProst (inhaled epoprostenol delivered via a dedicated delivery system)
Hydroxychloroquine	Antimalarial	Derivative of chloroquine	Inhibits lysosomal function	4, 8, 12 mg (nebulized) Up to 50 mg (nebulized) 20 mg (dry powder)
Plasminogen	Anticoagulant	Inert protein precursor	Thrombolytic	10 mg in 2 mL sterile water, twice daily (nebulized)
Modified Angiotensin-Converting Enzyme	Antiviral	Metallopeptidase	Regulates renin-angiotensin	Not available

Drug	Category	Chemical Nature	Mode of Action	Inhaled Dose and Formulation/Device
2			system and binds the viral spike protein and, thereby, neutralizes SARS-CoV-2	
Interferon-β	Antiviral agent	Signaling proteins	Protease inhibitor	6 mIU of IFN-β
Anti-Microbial Colloidal Silver Formulations	Antimicrobial	Nano-sized clusters of silver atoms	Destabilizes the cell membrane	10 µg/mL (ultrasonic mesh nebulizer)
Unfractionated heparin (UFH)	Anticoagulant	Sulfur-rich glycosaminoglycan	Inhibit factor Xa and factor IIa	25,000 IU/kg (Aeroneb Pro Nebulizer)
Salinomycin	Antibacterial agents	Polyketide	Inhibits endosomal acidification	Not available
Ivermectin	Antiparasitic drug	Macrocyclic lactone	Nuclear transport inhibitor	380 mg/m^3 (nebulizer)d, dose in rats, no studies in humans)
Niclosamide	Antiparasitic agents	Benzamide	SKP2 inhibitor	Not yet released

- **Remdesivir**

Remdesivir is a broad-spectrum antiviral drug with *in-vitro* activity against a variety of viruses.

As a result, SARS-CoV-2 was cleared for emergency use. To maximize delivery to the lung, where SARS-CoV-2 replication occurs, Shakijpijarna et al. developed remdesivir as a dry powder inhalation utilizing thin-film freezing (TFF) technology. When TFF is aerosolized from a passive dry powder inhaler, it forms brittle matrix nanostructured aggregates that are sheared into respirable low-density microparticles. Vartak et al. used cholesterol to create a stable aerosolized nanoliposomal carrier for remdesivir (AL-Rem). (A modified hydration approach yielded 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N [amino(polyethylene glycol)-2000] and DOPC (1,2-dioleoyl-sn-glycero-3-phosphocholine) as lipids. The created nanoliposomes (AL-Rem) have an ideal particle size of 71.46 1.35 nm, a good aerosol characteristic (fine particle fraction of 74.40 2.96%), and good drug entrapment efficiency.

Furthermore, this formulation showed low lung epithelial toxicity and long-acting drug release properties, which might benefit pulmonary administration and minimize dose frequency.

- **Ciclesonide[27, 33]**

Methylprednisolone, dexamethasone, hydrocortisone, and ciclesonide were among the systemic steroids examined. Ciclesonide is a safe medicine that is thought to be superior to conventional systemic corticosteroids in terms of slowing disease progression and symptom control, as well as having strong antiviral action against SRAS-CoV-2 because it predominantly stays in lung tissue and does not enter the bloodstream. Ciclesonide is an inhalation medication that is used to treat bronchial asthma and other bronchial inflammation. As a result, inhaled ciclesonide is adequate to reduce SARS-CoV-2-related inflammation. Iwabuchi et al. studied the effects of breathed nicotine. ciclesonide for three patients of COVID-19 pneumonia who were treated with ciclesonide inhalation and revealed the presence of the steroid in the lungs for a long time to regulate local inflammation as well as block virus growth via its antiviral activity Pharmaceutics 2021, 13, 1077 7 of 24.

- **Budesonide[26, 31]**

Budesonide is a long-acting corticosteroid used to treat asthma and COPD. Pre-treatment of human respiratory epithelial cells (human nasal (HNE) and tracheal (HTE) epithelial cells) with a combination of budesonide, glycopyrronium, and formoterol inhibited coronavirus HCoV-229E replication and cytokine generation in a recent *in-vitro* study. Currently, inhaled budesonide is being studied in clinical trials (NCT04355637, NCT04416399, NCT04193878, NCT04331470, and NCT04331054) alone and in combination with other medications such as formoterol, a _2 agonist, and levamisole, an immunostimulatory, to prevent an excessive cough.

In the lungs, there is a local immunological reaction. Inhaled budesonide was observed to reduce recovery time in COVID-19 patients over 50 who were treated at home and in community settings in phase three clinical investigation conducted by Oxford University. Within 7 days of the beginning of moderate COVID-19 symptoms, Ramakrishnan et al. undertook a randomized, open-label trial of inhaled budesonide in adults. The findings of this study show that early administration of inhaled budesonide reduces the need for emergency medical care and the time it takes to recover after a COVID-19 infection.

- **Furosemide[38, 43]**

Furosemide is a diuretic that is both safe and effective. It is also a small molecule medicine that is widely available. It can be breathed locally to the lungs; preclinical evidence and *in-vitro* experiments show it could be a candidate for repurposing as an aerosol treatment against COVID-19 immunopathology. Wang et al. evaluated furosemide's anti-inflammatory efficacy on several macrophage cell lines involved in innate immunity as part of its pre-clinical study. Inhaled furosemide was found to lower the levels of pro-inflammatory cytokines in this investigation. Furosemide is also a powerful inhibitor of interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF alpha) production, according to the researchers. In comparison to breathed saline, several clinical trials by Grogono et al. and Moosvai et al. found that inhaled furosemide eased air hunger in healthy people. Nishino et al. published another study.

Furosemide relieves the symptoms of dyspnea in healthy people, according to research. The results of this study demonstrated that inhaling furosemide increased overall breath-holding time and reduced respiratory pain during loaded breathing compared to inhaling a placebo.

Other investigations have found that breathed furosemide reduces bronchoconstriction and asthma episodes by acting through an anti-inflammatory mechanism.

It is critical to understand that administering furosemide to COVID-19 patients has two potential side effects: hypokalemia and electrolyte depletion as a result of SARS-CoV-2-induced pathology.

The diuretic effect of nebulized inhaled treatment, on the other hand, is expected to be insignificant. Another difficulty with employing a nebulized formulation is aerosol development, which can enhance viral spread if done without proper physical separation and protection. Despite this, breathed furosemide inhibits coughing and disease transmission.

- **Nitric Oxide (NO) and Epoprostenol [37, 41-43]**

Inhaled nitric oxide (iNO) and inhaled epoprostenol (iEPO) are two widely researched pulmonary vasodilators. Experience with acutely ill patients.

The respiratory distress syndrome (ARDS) suggests that iNO can significantly reduce the mean respiratory rate.

Improve the oxygenation of patients by lowering pulmonary arterial pressure. In addition, *in-vitro* evidence of direct antiviral action against SARS-CoV was investigated, and the genetic similarity between SARS-CoV and SARS-CoV-2 implies that they could be effective against SARS-CoV-2. The involvement of nitric oxide (NO) in the cardiovascular and immune systems is dependent on its concentration and manufacturing location. 2021, 13, 1077, Abnormal Pharmaceutics In vivo, 8 of 24 NO molecules are linked to illnesses, such as viral infection. NO levels were shown to be considerably lower in COVID-19 patients in recent research, suggesting a link between vascular dysfunction and immunological inflammation. iNO was utilized to treat severe hypoxemia during the 2003 SARS outbreak.

Because SARS-CoV-2 and SARS-CoV-1 have a similar infection pathway, the inhibition of SARS-CoV-2 by NO could be the same as that of SARS-CoV-1. High-dose pulmonary surfactant, inhaled nitric oxide, high-frequency oscillatory ventilation, and extracorporeal membrane oxygenation are also used to treat babies with severe ARDS. Patients with COVID-19 may benefit from this treatment as well.

In COVID-19 patients who were spontaneously breathing, Parikh et al. used iNO treatment.

For 2.1 days, the beginning dose of iNO was 30 parts per million.

More than half of the 39 spontaneously breathing COVID-19 patients treated with iNO therapy did not require mechanical ventilation after treatment, according to the findings. These data imply that iNO therapy could help COVID-19 patients avoid developing hypoxic respiratory failure. Clinical trials assessing the preventative and therapeutic effects of iNO against SARS-CoV-2 are being planned (NCT04305457, NCT04306393, NCT03331445, NCT04312243). In addition, the FDA authorized emergency enhanced access, allowing the company's iNO delivery technology (INOpulse®) to be used to treat COVID-19 right away.

- **Hydroxychloroquine[39,44]**

Antimalarial medications chloroquine (CQ) and hydroxychloroquine (HCQ) were among the first to be considered as prospective COVID-19 repurposable therapy options. The two medicines prevent the terminal glycosylation of ACE2 *in-vitro* without affecting the ACE2 cell surface, suggesting that they could be effective inhibitors of SARS-CoV-2 infections.

In the treatment of COVID-19, CQ and HCQ have been discussed as promising, cost-effective, and easily available medicines. *In-vitro* cell cultures revealed that HCQ is a more powerful inhibitor of SARS-CoV-2 infection than CQ. Both medicines, when used orally, can have serious side effects such as eye damage and psychological problems. The *in-vivo* application should be limited. To achieve appropriate therapeutic levels at the alveolar epithelial cells, the authors advised employing a small dose of aerosolized HCQ (2 - 4 mg per inhalation). The scientists also stated that utilizing a non-systemic low-dose aerosol would considerably lessen the unfavourable pharmacological effects of oral administration.

Kavanagh et al. highlighted an inhaled version of HCQ that has passed safety evaluations in clinical trials for asthma treatment, as well as how this technique could reduce side effects and enhance efficacy. The development of a basic formulation to phase two research would allow phase two trials in COVID-19 to be based on safety data.

To summarise all that has been said so far, one possibility for potentially improving HCQ efficacy at a lower dose is to give the medicine directly to the lungs as an inhaled formulation. In alveolar cells, HCQ was demonstrated to be efficient as an antiviral.

- **Plasminogen[42]**

The zymogen of plasmin, the major enzyme that dissolves fibrin clots and interacts with cell surfaces, is plasminogen. The plasminogen activators, which are protease systems, effectively activate it. Many pathological processes, such as fibrinolysis, wound healing, and infection, need the presence of plasminogen. Acute respiratory distress syndrome, the creation of a hyaline membrane primarily formed of fibrin, and "ground-glass" opacity have all been observed in the lungs of COVID-19 patients. As a result, Wu Y et al. looked into the involvement of plasminogen in COVID-19 patients' lung lesions and hypoxemia. Inhalation of plasminogen reduced pulmonary lesions in five clinically intermediate COVID-19 patients and oxygen saturation in six clinically severe COVID-19 patients (pharmaceutics 2021, 13, 1077 9 of 24). Finally, this research suggests that breathed plasminogen could be used to treat the pulmonary lesions and hypoxemia associated with COVID-19 infection.

- **Modified Angiotensin-Converting Enzyme 2 (ACE2) [41, 42]**

A functional receptor for SARS-CoV-1 and a strong receptor for SARS-CoV-2 has been found in ACE2, a metallopeptidase. ACE2 is a carboxypeptidase that potently degrades angiotensin II to angiotensin 1–7, a crucial role in the renin-angiotensin system (RAS). Recombinant ACE2 (rACE2) has been shown to protect against severe acute lung damage and acute Ang II-induced hypertension in previous studies. In mouse models, recombinant ACE2 (rACE2) has been shown to reduce Ang II-induced heart hypertrophy, cardiac dysfunction, and unfavorable myocardial remodeling, as well as renal oxidative stress, inflammation, and fibrosis. Based on ACE2's coronavirus receptor activity, Lei et al. suggested that ACE2, particularly the fusion protein, would have the ability to neutralize SARS-CoV-2.

By designing and producing a fusion protein (ACE2-Ig) constituted of the extracellular domain of human ACE2 coupled to the Fc domain of human IgG1, researchers evaluated the therapeutic potential of ACE2. Following their discovery that ACE2 fusion proteins attach to the RBD with high affinity, they evaluated the inhibitory efficacy of ACE2 fusion proteins against SARS-CoV-2 and compared it to SARS-CoV. Their findings revealed that both SARS-CoV and SARS-CoV-2 viruses were effectively eliminated by ACE2-Ig and mACE2-Ig.

Wrapp et al. found biophysical and structural evidence that the SARS-CoV-2 S protein has a higher affinity for ACE2 than the SARS-CoV-1 S protein. S. Ameratunga and colleagues.

have looked into using inhaled modified ACE2 as a decoy to prevent SARS-CoV-2 infection. They expected that swapping two amino acids in modified recombinant soluble human ACE2 molecules (shACE2) will boost the affinity for the RBD of inactivated SARS-CoV-2. The shACE2 was inhaled using a lower shear stress inhaler, such as a Respimat® inhaler, which reduces protein denaturation. Finally, the scientists suggest that inhaling modified shACE2 could change the course of the infection, delaying the death of the pulmonary epithelium and allowing for proper antiviral immune responses.

- **Interferon-b [26]**

Interferon-b is a cytokine that is produced in response to a viral infection and is principally responsible for driving innate immune responses in the human lung. SARS-CoV-2 prevents interferon from being released. SNG001 is a nebulizer-delivered inhalable formulation of recombinant interferon that is being developed to treat virus-induced lower respiratory tract infections. Inhalation administration will achieve a sufficient concentration of interferon-b in the lungs, resulting in a local antiviral response with little systemic exposure.

compared to a placebo in asthma patients with respiratory virus infection. Interferon-_ is a cytokine that is produced in response to a viral infection and is principally responsible for driving innate immune responses in the human lung. SARS-CoV-2 prevents interferon from being released. SNG001 is a nebulizer-delivered inhalable formulation of recombinant interferon that is being developed to treat virus-induced lower respiratory tract infections. Inhalation administration will achieve a sufficient concentration of interferon-_ in the lungs, resulting in a local antiviral response with little systemic exposure.

compared to a placebo in asthma patients with respiratory virus infection.

- **Anti-Microbial Colloidal Silver Formulations [2]**

Zachar et al. evaluated the antiviral and antibacterial effects of an inhaled silver nanoparticulate formulation for COVID-19 therapy, as well as the MIC of these silver nanoparticles in different parts of the respiratory system. The 3 - 7 nm nanoparticles are excellent at attaching to viruses and suppressing their contagious mechanisms. According to

the findings, providing a nanoparticulate colloidal solution at a concentration of 25 g/mL is successful in achieving target tissue concentration. The proposed formulations can be employed as an antiviral medication for the treatment of early-stage respiratory viral infections such as COVID-19/SARS-CoV-2, depending on the silver dosing regimen's safety information. Pharmaceutics 2021, 13, 1077 10 of 24.

- **Unfractionated Heparin (UFH) [1, 3]**

A trial to give UFH via nebulizers was shown in a study by van Haren et al. COVID-19-induced ARDS is characterized by diffuse alveolar injury and severe pulmonary coagulation activation, which results in fibrin deposition in the microvasculature and hyaline membrane development in the air sacs. Furthermore, SARS-CoV-2 patients had high levels of inflammatory cytokines in their plasma and bronchoalveolar lavage fluid, as well as severe coagulopathy. The authors observed that breathed UFH reduced pulmonary dead space, coagulation activity, and microvascular thrombosis in individuals with acute lung damage. In addition, UFH is anti-inflammatory, mucolytic, and anti-viral. It has been found to inactivate the SARS-CoV-2 virus and prevent its entry into mammalian cells, hence preventing SARS-CoV-2 pulmonary infection.

- **Salinomycin[5]**

Salinomycin, a carboxylic polyether ionophore discovered from *Streptomyces albus*, is a broad-spectrum antibiotic that has gotten a lot of attention for its ability to target cancer and viral infections selectively. Its antiviral action was mediated by endosomal acidification inhibition. It was recently found as a possible antiviral drug for the treatment of SARS-CoV-2, according to a recent study. Salinomycin's oral administration for the treatment of COVID-19, on the other hand, is hampered by poor absorption, low oral bioavailability, and off-target effects. Pindiprolu et al. recommended encapsulating salinomycin in nanostructured carriers and delivering them directly to the lungs as an appealing technique for the treatment of respiratory diseases such as SARS-CoV-2 infections to overcome these constraints.

- **Ivermectin [47, 48]**

Ivermectin is an anti-parasitic medicine that has shown anti-viral action *in-vitro* against a variety of DNA and RNA viruses, including SARS-CoV-2. It works by preventing the human immunodeficiency virus-1 (HIV-1) from interacting with the integrase protein (IN) and the

importin (IMP). A single dose of ivermectin reduced the multiplication of an Australian isolate of SARS-CoV-2 in Vero/hSLAM cells by 5000-fold, according to Caly et al. (2020). To establish a correct concentration at the site of infection, i.e. the respiratory system, a very high dose of medicine is necessary as an oral dosage form. As a result, it's thought that an inhaled form of ivermectin could transport the drug straight to the target. A phase two trial for inhaled ivermectin as a nasal spray (1 mL in each nostril two times) is now underway.

Tanta University, Egypt (daily) (NCT04510233).

- **Niclosamide [1, 4]**

Niclosamide, a narrow-spectrum anthelminthic medication, works by blocking mitochondrial oxidative phosphorylation. Several studies have suggested that niclosamide could be used to treat a variety of viruses, including coronaviruses. It's thought to work against SARS-CoV-2 by inhibiting SKP2 in the same way as MERS-CoV inhibits host cell autophagy (S-phase kinase-associated protein 2). Because of niclosamide's limited water solubility and absorption, it can't be given orally to get to the infection site. As a result, direct delivery of niclosamide to the lungs could circumvent the limits of oral administration and achieve large medication concentrations at the infection site, namely the lungs. Brunaugh et al. created niclosamide-containing composite particles.

Human lysozyme, an endogenous protein, is used to deliver drugs to the lungs by inhalation.

The co-formulation of niclosamide with lysozyme is four-fold, according to a study.

When compared to niclosamide alone, it is more effective against coronaviruses. According to a recent study, Jara et al. created a niclosamide dry powder formulation that included.

Using a thin-film freezing approach, hydrophilic excipients, mannitol, and leucine were frozen.

With an 86 percent fine particle fraction, these powders are appropriate for deep lung delivery Pharmaceutics 2021, 13, 1077 11 of 24 Pharmaceutics 2021, 13, 1077 11 of 24 Pharmaceutics 2021, 13, 1077 11 of 24 Pharmaceutics 2021, 13, 1077 11 of 24 Pharmaceutics 2021, 13, 1077 11 of 24 Pharmaceutics Furthermore, pharmacokinetic research in a Syrian hamster model showed that a single inhalation dosage of the formulation keeps drug concentrations above IC90 for at least 24 hours.

BENEFITS OF PULMONARY DRUG DELIVERY[2]

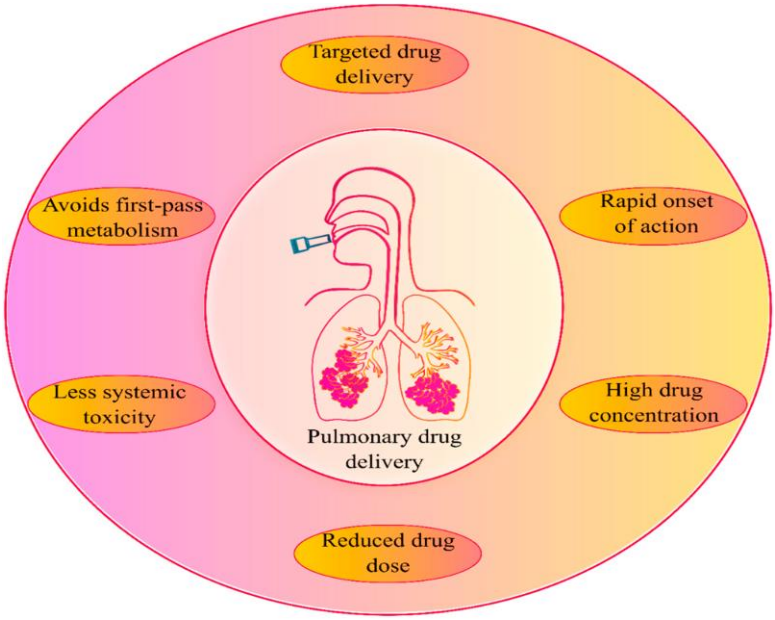

Figure No. 6: Benefits of Pulmonary Drug Delivery[2]

REFERENCES:

1. Intranasal Antiviral Drug Delivery and Coronavirus Disease 2019 (COVID-19): A State of the Art ReviewThomas S. Higgins, MD, MSPH, Arthur W. Wu, MD, Elisa A. Illing, MD, Kevin J. Sokoloski, PhD, Bree A. Weaver, MD, Benjamin P. Anthony, MD, Nathan Hughes, PharmD, Jonathan Y. Ting, MD, MS, MBA
2. Inhalation Delivery for the Treatment and Prevention ofCOVID-19 Infection,Basanth Babu Eedara 1, Wafaa Alabsi 1,2, David Encinas-Basurto 1,Robin Polt 2, Julie G. Ledford and Heidi M. Mansour
3. Omolo, C.A.; Soni, N.; Fasiku, V.O.; Mackraj, I.; Govender, T. Update on therapeutic approaches and emerging therapies forSARS-CoV-2 virus. Eur. J. Pharmacol. **2020**, 883, 173348. [CrossRef]
4. Chung, J.Y.; Thone, M.N.; Kwon, Y.J. COVID-19 vaccines: The status and perspectives in delivery points of view. Adv. DrugDeliv. Rev. **2021**, 170, 1–25. [CrossRef]
5. Huang, C.;Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Zhang, L.; Fan, G.; Xu, J.; Gu, X. Clinical features of patients infected with2019 novel coronavirus in Wuhan, China. Lancet **2020**, 395, 497–506. [CrossRef]
6. Coronavirus Disease (COVID-19) Dashboard. World Health Organization website. Available online: https://covid19.who.int/(accessed on 18 June 2021).
7. Bhavana, V.; Thakor, P.; Singh, S.B.; Mehra, N.K. COVID-19: Pathophysiology, treatment options, nanotechnology approaches,and research agenda to combating the SARS-CoV2 pandemic. Life Sci. **2020**, 261, 118336. [CrossRef]
8. Edwards, D.; Hickey, A.; Batycky, R.; Griel, L.; Lipp, M.; Dehaan,W.; Clarke, R.; Hava, D.; Perry, J.; Laurenzi, B.; et al. A Newnatural defense against airborne pathogens. QRB Discov. **2020**, 1, e5. [CrossRef]
9. Tay, M.Z.; Poh, C.M.; Rénia, L.; MacAry, P.A.; Ng, L.F.P. The trinity of COVID-19: Immunity, inflammation and intervention. Nat.Rev. Immunol. **2020**, 20, 363–374. [CrossRef] [PubMed]
10. Abdellatif, A.A.H.; Tawfeek, H.M.; Abdelfattah, A.; El-Saber Batiha, G.; Hetta, H.F. Recent updates in COVID-19 with emphasison inhalation therapeutics: Nanostructured and targeting systems. J. Drug Deliv. Sci. Technol. **2021**, 63, 102435. [CrossRef][PubMed]
11. Mitchell, J.P.; Berlinski, A.; Canisius, S.; Cipolla, D.; Dolovich, M.B.; Gonda, I.; Hochhaus, G.; Kadrichu, N.; Lyapustina, S.;Mansour, H.M. Urgent appeal from International Society for Aerosols in Medicine

(ISAM) during COVID-19: Clinical decisionmakers and governmental agencies should consider the inhaled route of administration: A statement from the ISAM regulatoryand standardization issues networking group. J. Aerosol Med. Pulm. Drug Deliv. **2020**, 33, 235–238. [CrossRef] [PubMed]

12. Hickey, A.J. Back to the future: Inhaled drug products. J. Pharm. Sci. **2013**, 102, 1165–1172. [CrossRef] [PubMed]
13. Rau, J.L. The inhalation of drugs: Advantages and problems. Respir. Care **2005**, 50, 367–382.
14. Eedara, B.B.; Tucker, I.G.; Das, S.C. In vitro dissolution testing of respirable size anti-tubercular drug particles using a smallvolume dissolution apparatus. Int. J. Pharm. **2019**, 559, 235–244. [CrossRef]
15. Eedara, B.B.; Rangnekar, B.; Doyle, C.; Cavallaro, A.; Das, S.C. The influence of surface active l-leucine and 1,2-dipalmitoyl-snglycero-3-phosphatidylcholine (DPPC) in the improvement of aerosolization of pyrazinamide and moxifloxacin co-spray driedpowders. Int. J. Pharm. **2018**, 542, 72–81. [CrossRef]
16. Eedara, B.B.; Rangnekar, B.; Sinha, S.; Doyle, C.; Cavallaro, A.; Das, S.C. Development and characterization of high payload combination dry powders of anti-tubercular drugs for treating pulmonary tuberculosis. Eur. J. Pharm. Sci. **2018**, 118, 216–226.[CrossRef] [PubMed]
17. Eedara, B.B.; Tucker, I.G.; Das, S.C. Phospholipid-based pyrazinamide spray-dried inhalable powders for treating tuberculosis.Int. J. Pharm. **2016**, 506, 174–183. [CrossRef] [PubMed]
18. Eedara, B.B.; Tucker, I.G.; Zujovic, Z.D.; Rades, T.; Price, J.R.; Das, S.C. Crystalline adduct of moxifloxacin with trans-cinnamic acid to reduce the aqueous solubility and dissolution rate for improved residence time in the lungs. Eur. J. Pharm. Sci. **2019**, 136,104961. [CrossRef] [PubMed]
19. Rangnekar, B.; Momin, M.A.M.; Eedara, B.B.; Sinha, S.; Das, S.C. Bedaquiline containing triple combination powder for inhalationto treat drug-resistant tuberculosis. Int. J. Pharm. **2019**, 570, 118689. [CrossRef]
20. Tu, Y.-F.; Chien, C.-S.; Yarmishyn, A.A.; Lin, Y.-Y.; Luo, Y.-H.; Lin, Y.-T.; Lai,W.-Y.; Yang, D.-M.; Chou, S.-J.; Yang, Y.-P.; et al. Areview of SARS-CoV-2 and the ongoing clinical trials. Int. J. Mol. Sci. **2020**, 21, 2657. [CrossRef]
21. Fang,W.; Jiang, J.; Su, L.; Shu, T.; Liu, H.; Lai, S.; Ghiladi, R.A.;Wang, J. The role of NO in COVID-19 and potential therapeuticstrategies. Free Radic. Biol. Med. **2021**, 163, 153–162. [CrossRef]
22. Wang, Z.; Wang, Y.; Vilekar, P.; Yang, S.-P.; Gupta, M.; Oh, M.I.; Meek, A.; Doyle, L.; Villar, L.; Brennecke, A. Small moleculetherapeutics for COVID-19: Repurposing of inhaled furosemide. PeerJ **2020**, 8, e9533.
23. Lotfi, M.; Hamblin, M.R.; Rezaei, N. COVID-19: Transmission, prevention, andpotential therapeutic opportunities. Clin. Chim.Acta **2020**, 508, 254–266.
24. Hu, B.; Guo, H.; Zhou, P.; Shi, Z.-L. Characteristics of SARS-CoV-2 and COVID-19. Nat. Rev. Microbiol. **2020**, 19, 141–154.
25. Wrapp, D.;Wang, N.; Corbett, K.S.; Goldsmith, J.A.; Hsieh, C.-L.; Abiona, O.; Graham, B.S.; McLellan, J.S. Cryo-EM structure ofthe 2019-nCoV spike in the prefusion conformation. Science **2020**, 367, 1260–1263.26. Amanat, F.; Krammer, F. SARS-CoV-2 vaccines: Status report. Immunity **2020**, 52, 583–589.
26. Van Doremalen, N.; Bushmaker, T.; Morris, D.H.; Holbrook, M.G.; Gamble, A.; Williamson, B.N.; Tamin, A.; Harcourt, J.L.;Thornburg, N.J.; Gerber, S.I. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N. Engl. J. Med. **2020**,
27. Cevik, M.; Tate, M.; Lloyd, O.; Maraolo, A.E.; Schafers, J.; Ho, A. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics,duration of viral shedding, and infectiousness: A systematic review and meta-analysis. Lancet Microbe **2021**, 2, e13–e22.
28. Stein, S.W.; Thiel, C.G. The history of therapeutic aerosols: A chronological review. J. Aerosol Med. Pulm. Drug Deliv. **2017**, 30, 20–41.
29. Hickey, A.J. Emerging trends in inhaled drug delivery. Adv. Drug Deliv. Rev. **2020**, 157, 63–70.
30. Pilcer, G.; Amighi, K. Formulation strategy and use of excipients in pulmonary drug delivery. Int. J. Pharm. **2010**, 392, 1–19.
31. Alabsi, W.; Al-Obeidi, F.A.; Polt, R.; Mansour, H.M. Organic solution advanced spray-dried microparticulate/nanoparticulate drypowders of lactomorphin for respiratory delivery: Physicochemical characterization, in vitro aerosol dispersion, and cellular studies. Pharmaceutics **2020**, 13, 26. [CrossRef]

32. Eedara, B.B.; Alabsi, W.; Encinas-Basurto, D.; Polt, R.; Mansour, H.M. Spray-dried inhalable powder formulations of therapeuticproteins and peptides. AAPS PharmSciTech **2021**, 22, 185.
33. Sahakijpijarn, S.; Moon, C.; Koleng, J.J.; Christensen, D.J.; Williams III, R.O. Development of remdesivir as a dry powder forinhalation by thin film freezing. Pharmaceutics **2020**, 12, 1002.
34. Vartak, R.; Patil, S.M.; Saraswat, A.; Patki, M.; Kunda, N.K.; Patel, K. Aerosolized nanoliposomal carrier of remdesivir: Aneffective alternative for COVID-19 treatment in vitro. Nanomedicine **2021**, 16, 1187–1202.
35. Matsuyama, S.; Kawase, M.; Nao, N.; Shirato, K.; Ujike, M.; Kamitani,W.; Shimojima, M.; Fukushi, S. The inhaled corticosteroidciclesonide blocks coronavirus RNA replication by targeting viral NSP15. BioRxiv **2020**.
36. Alexander, TH, Davidson, TM. Intranasal zinc and anosmia: the zinc-induced anosmia syndrome. Laryngoscope. 2006;116(2):217-220.Google Scholar | Crossref | Medline
37. Skalny, A, Rink, L, Ajsuvakova, O, et al. Zinc and respiratory tract infections: perspectives for COVID-19 (Review). Int J Mol Med. 2020;46(1):17-26. Google Scholar | Medline
38. Geisthoff, U, Blum, A, Ruppclassen, M, Plinkert, P. Lipid-based nose ointment for allergic rhinitis. Otolaryngol Head Neck Surg. 2005;133:754-761.Google Scholar | SAGE Journals | ISI
39. Wang, X, Liu, G, Ma, J, et al. In situ gel-forming system: an attractive alternative for nasal drug delivery. Crit Rev Ther Drug Carrier Syst 2013; 30(5): 411-34. Google Scholar | Crossref | Medline
40. Dayal, P, Shaik, MS, Singh, M. Evaluation of different parameters that affect droplet-size distribution from nasal sprays using the Malvern Spraytec. J Pharm Sci. 2004;93:1725-1742.Google Scholar | Crossref | Medline | ISI
41. Aderibigbe, BA, Naki, T. Design and efficacy of nanogels formulations for intranasal administration. Molecules. 2018;23.Google Scholar
42. Efficacy of "Essential Iodine Drops" against Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2)
43. Zoltán Köntös ,Dietz L, Horve PF, Coil DA, Fretz M, Eisen JA, Van Den Wymelenberg K. 2020. 2019 Novel Coronavirus (COVID-19) Pandemic: Built Environment Considerations To Reduce Transmission. mSystems 5:e00245–20. pmid:32265315
44. Santarpia J, Rivera D, Herrera V, Morwitzer M, Creager H, Santarpia G, et al. 2020. Transmission Potential of SARS-CoV-2 in Viral Shedding Observed at the University of Nebraska Medical Center
45. van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. 2020. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. The New England journal of medicine 382:1564–1567. pmid:32182409
46. Povidone Iodine Mouthwash, Gargle, and Nasal Spray to Reduce Nasopharyngeal Viral Load in Patients With COVID-19A Randomized Clinical TrialJeremy Guenezan, MD[1]; Magali Garcia, MD, PhD[2]; Deidre Strasters, MD[1]; et al Clément Jousselin, PhD[2]; Nicolas Lévêque, PharmD, PhD[2]; Denis Frasca, MD, PhD[3]; Olivier Mimoz, MD, PhD[1],[1]Emergency Department, University Hospital of Poitiers, Poitiers, France,Virology laboratory, University Hospital of Poitiers, Poitiers, France, Department of Anesthesia, Intensive Care and Perioperative Medicine, University Hospital of Poitiers, Poitiers, France.
47. Wiersinga WJ,Rhodes Ac,Cheng ACPeacock SJPrescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): A Review. *JAMA*. 2020;324(8):782-793. doi:10.1001/jama.2020.12839
48. Frank S, Brown SM, Capriotti JA, Westover JB, Pelletier JS, Tessema B. In vitro efficacy of a povidone-iodine nasal antiseptic for rapid inactivation of SARS-CoV-2. *JAMA Otolaryngol Head Neck Surg*. 2020;146(11):1-5. doi:10.1001/jamaoto.2020.3053
49. Etievant S, Bal A, Escuret V, et al. Performance assessment of SARS-CoV-2 PCR assays developed by WHO referral laboratories. *J Clin Med*. 2020;9(6):1871. doi:10.3390/jcm9061871