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Review Article

NICLOSAMIDE: A POTENTIAL TREATMENT OPTION FOR COVID-19

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ABSTRACT

Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) poses a global health hazard due to its rapid dissemination and limited treatment options. Identification of possible treatments that may kill the virus, speed up the recovery, or reduce the case fatality rate is a need of hour. However, developing and producing particular COVID-19 medicines and vaccines is a time-consuming process with possibilities of clinical failures due to safety or efficacy issue. Medication repositioning is a safer and quicker approach for dealing with the COVID-19 worldwide threat right now. Out of 48 FDA-approved medicines tested against SARS-CoV-2, niclosamide is one amongst few that has shown potential *in vitro* antiviral activity against SARS-CoV-2. However, the currently available oral conventional formulation of niclosamide results in systemic medication levels those are unsatisfactory to inhibit SARS-CoV-2. Hence, various formulation strategies have been adapted in order to achieve an optimum therapeutic outcome of niclosamide when delivered via oral, inhalation, and intranasal routes. Some of these formulations are presently undergoing clinical trials. The current review focuses on the mechanisms of action of niclosamide and its repurposing effectiveness against COVID-19. The delivery strategies to improve its bioavailability have been overviewed. The recently completed and ongoing clinical trials have also been summarized.

Keywords: SARS-CoV-2, COVID-19, Niclosamide, Oral formulation, Repurposed drug, Oral bioavailability, Clinical trial

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INTRODUCTION

The human population of the 21st century is engulfed in a pandemic caused by the emerging SARS-CoV-2, termed COVID-19, which poses a threat to public health around the world [1]. Numeral ways and rules were adopted to prevent, diagnose and cure the disease [2]. The disease was first discovered in Wuhan towards the end of 2019 and then quickly spread across the globe. On March 11, 2020, the World Health Organization (WHO) announced COVID-19 to be a pandemic. COVID-19 is extremely transmissible compared to earlier strains like Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), which afflicted East Asian countries in the early 2000s [3]. Coronaviruses are pleomorphic, enveloped, positive sense, 27–32 kb large RNA viruses that cause respiratory and enteric infections in humans and other animals [4]. It has a 120 nm diameter, roughly. In electron micrographs, the virus's envelope is seen as a discrete pair of electron-dense shells [5]. Coronaviruses are divided into four categories: delta, gamma, beta, and alpha coronaviruses. Alpha and beta coronaviruses are found particularly in bats, while gamma and delta coronaviruses are found in pigs and birds. They are the primary cause of respiratory infections and disorders, which range from the common cold to more serious illnesses such as pneumonia, lymphopenia, severe chest symptoms [6]. There is a lot of published literature about the management of COVID-19 cases [7]. Currently, the COVID-19 epidemic has killed more people than any of the other pandemics previously mentioned, as well as crippled the world's healthcare system and economy. COVID-19 infection prevention and therapy currently have limited treatment and vaccine options, and outbreaks are projected to persist beyond 2025. For COVID-19 infection prevention, vaccines from Pfizer/BioNTech, Moderna, Johnson and Johnson's Janssen, and AstraZeneca are approved and recommended [8].

To fully address the ongoing pandemic, patients and physicians throughout the world must have quicker and affordable access to medicines. Though, new drug discovery is the most appropriate strategy to effectively combat the virus, it poses the challenge of long waiting time, higher development costs, and also the risks of failure in safety and/or efficacy during the clinical phase. In this context, drug repurposing becomes a quicker, cost-effective and viable option in which previously approved drug candidates that have failed, been abandoned, or been in clinical practice for some other indication are reintroduced for a new purpose [9].

Drug repurposing, which involves using 'old' medicines to treat 'new' diseases, is a promising strategy to drug development. Sizable clinical knowledge and a well-established track record of safety of the old drug helps to expedite the process of approval of these drugs for the new indications. Considering these advantages, 48 FDA-approved medicines were tested againstSARS-CoV-2. [10]. Already reported antiviral activity of niclosamide against SARS and MERS-CoV led to its inclusion in the list of the 48 medicines [11]. Of these, 24 drugs showed potential antiviral activity against SARS-CoV-2, with IC_{50} values ranging from 0.1 to 10 µM. Niclosamide with $IC_{50}$of 0.28 µM was one amongst these medicines. As a result, niclosamide might be a viable COVID-19 medication candidate. The present review gives an account of the mechanisms by which niclosamide curbs the SARS–CoV-2 infection, formulation strategies undertaken so far to improve its efficacy via different routes of administration and the clinical studies for treating COVID-19 infection. For compiling the review, databases such as PubMed, ScienceDirect, Google Scholar, and websites of WHO and Clinical trial registry were explored. Keywords such as SARS-CoV-2, COVID-19, Niclosamide, Oral formulation, repurposed drug, Oral bioavailability, Clinical trial were used to collect the research articles during the time span from 1982 till date.

Niclosamide–An old drug with a new life/a repurposed drug

Drug repurposing provides patients with access to medications in a quick, affordable, and convenient manner [12]. Drug repositioning is a unique idea that seeks to find new uses for medications that have already received approval and are on the market, either for the treatment of unforeseen diseases or because they failed to develop successfully [13]. Niclosamide [5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide] is a pleiotropic anthelminthic medication. In 1953, Bayer chemotherapeutic research scientists developed niclosamide as a molluscicide to kill snails, and it was sold as Bayluscide®. The drug was later shown to be effective against human tapeworm (cestoda) infection by Bayer scientists, and it was introduced as Yomesan for human usage in 1962 [12, 13]. Niclosamide was authorised by the US Food and Drug Administration in 1982 for use in humans to treat tapeworm infection, and it is on the WHO's list of essential medicines [16]. Niclosamide exerts its anticestodal action by decreasing oxidative phosphorylation in the mitochondria and increasing adenosine triphosphatase activity [14]. It has been used to treat millions of people in a safe manner.

As a result of repurposing screens undertaken during the past several years, niclosamide has been discovered as a multifunctional medication [15, 16]. Cancer, bacterial and viral infections, metabolic diseases such as Type II diabetes, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, artery constriction, endometriosis, neuropathic pain, rheumatoid arthritis, sclerodermatous graft-versus-host disease, and systemic sclerosis are all examples of these diseases and symptoms [17–22]. It has particularly drawn attention in the treatment of various cancers, including lung cancer, nasopharyngeal cancer and breast cancer [25]. As a result, it has been proven to be an "ancient drug with a new life." Several studies have shown that niclosamide has wide antiviral activity against SARS-CoV-2 infection [9-10, 24, 25].

In 2004, Wu *et al.* discovered that niclosamide in 1.5 µM micromolar concentrations had an inhibitory impact on SARS-CoV multiplication in Vero E6 cells [23]. Later on, Gassen *et al.* proved 1000 fold higher activity of niclosamide against MERS-CoV viral multiplication. Increasing host cell autophagy in MERS-CoV by inhibiting S-phase kinase-associated protein 2(SKP2) activity was the deduced mechanism of niclosamide action [26]. In a report published in 2020, it was shown to exhibit significant activity against SARS-CoV-2, with IC_{50}value of 0.28 µM (~100 ng/ml) and IC_{100}value 1 µM (~300 ng/ml), respectively. Arshad *et al.* estimated a niclosamide IC_{90} of 153.7 ng/ml based on the results given by [10, 27]. This research initiated the studies of niclosamide in the treatment of the COVID pandemic.

Plausible antiviral mechanisms of action of niclosamide against SARS-Cov-2

Niclosamide could act through the following major pharmacological pathways-

1) Blocking of endocytosis of SARS-CoV-2 virus

SARS-CoV-2 spikes have been shown to attach to the angiotensin-converting enzyme-2 (ACE-2) receptors and infect host cells. Cathepsin L proteolysis occurs within endosomes following receptor engagement and causes conformational changes in S-protein for viral entry into host cells [28, 29]. Niclosamide can stop SARS-CoV2 from entering into the host cells by inhibiting the pH-dependent endocytic pathway [29]. In earlier studies, niclosamide was linked to pH-dependent endocytosis of the human rhinovirus (HRV) and influenza [30]. This same mechanism might be involved in its activities against SAR-CoV-2. However, the exact method by which niclosamide inhibits the ACE-2 protein is yet unknown [31].

2) Inhibition of the autophagy of SARS-CoV-2 through S-Phase kinase-associated protein 2 (SKP2) blocking.

The work carried out by Gassen*et al.* revealed niclosamide-induced inhibition of SKP2 and subsequent autophagy that decreases MERS-CoV replication and inhibits viral particle spread within cells. The same mechanism could be attributed to SARS-CoV-2 inhibition, owing to the fact that both viruses require the same ACE-2 protein for entering into the host cells [26, 32].

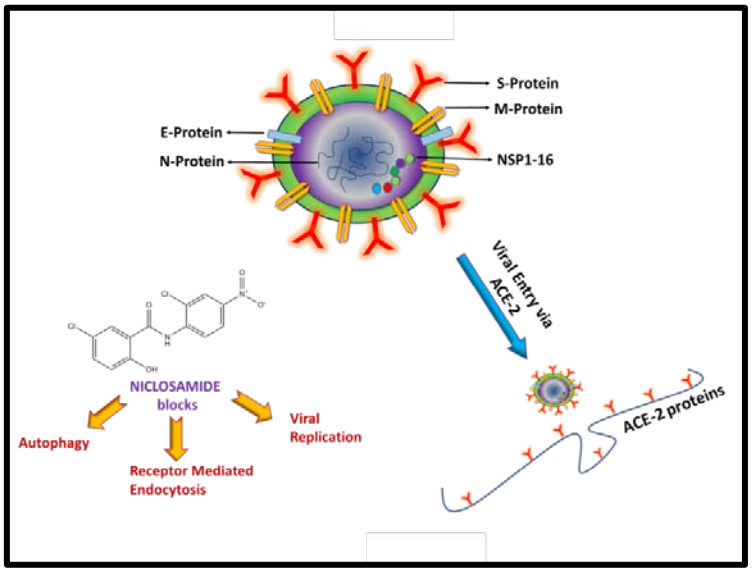

Fig. 1: Niclosamide's antiviral mode of action against SARS-Cov-2 [31]

Oral bioavailability improvement studies of niclosamide to treat covid 19

Under ambient conditions, niclosamide has an aqueous solubility of 0.23–1.6 µg ml^{-1}. The currently available niclosamide oral formulations are effective in treating worm infestations locally in the gastrointestinal tract. The most common way to provide drugs is through oral administration. The suggested method of administration is oral to ensure patient compliance. Due to its simplicity of administration, the oral route has grown in popularity over the past few decades [33]. Poor solubility and oral bioavailability of niclosamide offsets its significant repurposing potential [34, 35]. Hence, several techniques such as co-crystals [35–37], solid lipid nanoparticles [35], dendrimers [38], micelles [8, 39], nanosuspensions [40], nanoparticles [41], lipid emulsions [42], and nanocrystals [43] have been explored so far to improve niclosamide's water solubility and bioavailability in order to harness its potential in treating various cancers, metabolic disorders as well as bacterial and viral infections. The following section includes some of the most currently used approaches to improve the delivery of niclosamide for efficacious treatment of COVID-19 [44].

Choi and Piao *et al.*, developed hydrotalcite (HT) nanohybrids of niclosamide. Niclosamide-loaded hydrotalcite composite nanohybrids were then coated with Tween 60 or HPMC to improve emulsification in the GI tract. Dehydrated HT (DHT), having a higher surface area compared to intact HT was used as a carrier for preparing the formulation, The substituents on hydroxypropyl methylcellulose (HPMC) influence emulsion stability through viscosity effects, the formation of a gel network The optimized formulation with particle size less than 300 nm was orally administered to rats for studying the pharmacokinetic parameters. Niclosamide–dehydrated HT/Tween 60 (50 mg/kg) formulation resulted in a C_{max} of 1350.37±613.98 ng/ml at the t_{max} of 0.24 h. This was much greater than the neat niclosamide's C_{max} (155.27±39.92 ng/ml) at the t_{max} of 4 h. Furthermore, a single oral dose of niclosamide–dehydrated HT/HPMC (200 mg/kg) resulted in niclosamide plasma concentrations as high as 18,928.63±2934.34

ng/ml. The plasma concentration of drug was maintained above its IC_{50} (~100 ng/ml) for more than 24 h. After coating with Tween 60 or HPMC, the NIC-DHT nanohybrids demonstrated optimal particle sizes of around 300 nm with excellent PK profiles. Based on this, NIC-DHT/Tween 60 and NIC-DHT/HPMC oral formulations were created on the idea that non-ionic coating polymers and HT could enhance PK characteristics [45].

Seungjin Yu *et al.*, presented a novel hybrid drug delivery system composed of niclosamide, montmorillonite (MMT), and Tween 60 to solve the drug solubility issues. Niclosamide molecules were immobilized in the interlayer space of cationic clay, MMT, to create niclosamide–MMT hybrids, which were then surface-coated with Tween 60. The oral bioavailability of niclosamide–MMT (1:1) hybrids was compared to Yomesan®, a commercially available niclosamide tablet formulation, in an *in vivo* pharmacokinetic investigation. C_{max} (315.45±124.64 ng/ml), AUC_{0-t} (1751.02±421.77 ng·h/ml), and $AUC_{0-\infty}$ (1766.90±423.85 ng·h/ml) for niclosamide were 2.0-fold, 1.6-fold, and 1.5-fold higher for the developed formulation than for Yomesan®, respectively. Improved solubility of niclosamide in the presence of the surfactant and sustained release from MMT intercalation improved the bioavailability of the drug significantly [46].

Wang and colleagues produced a lipid nano particle formulation of niclosamide to study its *in vitro* efficacy against SARS-CoV-2 infection in Vero E6 and ACE2-expressing lung epithelial cells. Niclosamide: di-stearoyl phosphatidyl ethanolamine (DSPE)-PEG2000 in a weight ratio of 1.19:1. The formulation had a drug loading capacity of 54.3 %. With 0.154 μM IC_{50} and 1.38 μM IC_{90} and a selectivity index of 137, the formulation exhibited antiviral effectiveness against SARS-CoV-2 infection in human lung epithelial cell line (A549 cells) expressing human ACE2. The formulation was adequately stable, easy to prepare with FDA-approved excipients, and thus showed translational potential [47].

For improving the apparent solubility and oral bioavailability of niclosamide, hot-melt extrusion technique was employed by Jara *et al.* Amorphous solid dispersions of niclosamide were prepared using poly (1-vinylpyrrolidone-co-vinyl acetate) (PVP–VA-niclosamide)-TPGS blend in 60:35:5 ratio and processed using HME at 150 rpm and 180 °C. Dissolution testing for two hours in the bio-relevant FaSSIF media revealed 60 times greater apparent solubility of niclosamide amorphous solid dispersions as compared to the crystalline niclosamide anhydrate. In a rat model, pharmacokinetic investigations indicated more than2-fold higher bioavailability of niclosamide ASD when compared to niclosamide anhydrate [48].

Pulmonary delivery studies of niclosamide

The SARS-CoV-2 virus primarily affects the lungs, with a preference for alveolar macrophages and pneumocytes (type I and II) [49]. The virus causes breathing problems, acute respiratory distress syndrome, and pneumonia, among other problems [50, 51]. Direct drug administration to the respiratory tract provides an alternative to niclosamide's significant bioavailability limitation, and it might be used to address the major location of SARS-CoV-2 infection and dissemination. After 24 h of treatment of *Pseudomonas aeruginosa* lung infections in cystic fibrosis (CF), niclosamide has been found to be safe for inhalation. The provided experimental data supports continued research into niclosamide, an antivirulence medication, as a potential CF therapy and calls for research of the inhalable drug's anti-*P. aeruginosa* activity niclosamide formulations were created in this article using animal models of pneumonia in the lungs. Using a well-known medication again niclosamide, may be used to treat lung infections in CF patients through inhalation. also lead to a significant decrease in the price of the product compared to the creation of new chemical entities [40]. The following section refers to a few studies conducted for repurposing niclosamide in treating COVID-19.

Brunaugh *et al.* established that niclosamide-human lysozyme (NIC-hLYS) was effective in the treatment of COVID-19 *in vitro* and *in vivo*. Through the use of hLYS as a carrier molecule, a niclosamide powder formulation was created for administration in the form of dry powder inhaler, nebulizer, and nasal spray. In comparison to niclosamide particles alone, co-formulation of the cationic, endogenous protein hLYS with micronized niclosamide resulted in a 4-fold increased potency against coronaviruses. The formulation also showed a 2-fold higher potency against methicillin-resistant *Staphylococcus aureus,* a common cause of secondary bacterial pneumonia associated with COVID-19. The inflammatory cytokines TNF-α and IL-6, which have been linked to the development of more severe COVID-19, were suppressed by the NIC-hLYS particles, whereas the inflammatory cytokine IL-1b was elevated, perhaps contributing to increased antiviral activity [52]. NIC formulation that can be administered using 3 model DPI, Nasal spray and nebuliser to achieve this aim we utilise human lysozymes an endogenous protein in upper and lower respiratory tract as carrier system for delivery of NIC to the air way.

Miguel O. Jara *et al.* created the niclosamide dry powder formulation for inhalation as a COVID-19 infection treatment. Thin film freezing was used to create a dry powder version of niclosamide, which was then given as an inhalation to the rats and hamsters. With a fine particle fraction of 86.0 %, a mass median aerodynamic diameter of 1.11 μm, and a geometric standard deviation of 2.84, this niclosamide inhalation powder produced satisfactory aerosol performance. After pulmonary administration in rats, the niclosamide inhalation powder was found to be safe, A single dose delivered by inhalation in Syrian golden hamsters led to persistence of drug concentrations larger than the published IC_{50} and IC_{90} for SARS-CoV-2 in the lungs for at least 24 h [53].

Parenteral delivery of niclosamide in COVID-19 treatment

Some researchers are working on developing an injectable anti-COVID 19formulation to allow for rapid administration into the bloodstream, where the damaged endothelium glycocalyx found in COVID-19 patients is [54] expected to allow for increased niclosamide medication absorption from the injected formulation.

Hobson *et al.* developed a long-acting injectable solid dispersible nanoparticulate formulation (SDN) of niclosamide. SDNs are stabilised nanoparticles made completely of API that do not require nanocarrier encapsulation. As a result, they give a therapeutic alternative for high injectable medication concentrations in the water while reducing injection volume.

a) An aqueous solution containing stabilisers and sugars is pumped into niclosamide solution;

b) The good solvent is diluted by the poor aqueous solvent, and particle growth is stopped by stabilisers, in this model of the nucleation and growth of niclosamide nanoparticles.

c) After sonication, the nanoparticle dispersion is pumped into a spray drier.

d) Spray-dried powder contains niclosamide nanoparticles and water-soluble excipients; the nanoparticles are redispersed in aqueous media for injection.

Soluble excipients and niclosamide nanoparticles; nanoparticles are redispersed in aqueous media for injection. Studies of the SDN were undertaken for 28 d in Sprague Dawley rats to determine the release kinetics of three distinct intramuscular dosages. All of the injected doses attained C_{max} within 3 h of administration. The bioavailability rose with increasing doses, C_{max} values of 1408.6, 2041.3, 3125.3 ng ml^{-1} and AUC of 28955, 55734, 74584 ng h ml^{-1}were observed for 50, 100, and 200 mg kg^{-1}doses. This formulation could be kept in a solid form, then reconstituted with water and utilised as a long-acting injectable for a month's worth of drug exposure [55].

Bovine serum albumin (BSA)-coated zein-niclosamide nanohybrids were developed by Hobson *et al.* as an injectable nanomedicine treatment for COVID-19. The nanohybrid was reported to have a particle size of less than 200 nm, with good colloidal stability and 60 % drug released after 24 h in pH 7.4 buffer. Furthermore, in serum circumstances, the nanohybrid demonstrated improved drug release behaviour, indicating that such a hybrid drug delivery system might be extremely useful in treating COVID-19 patients [44].

Clinical trials

The majority of the evidence for nicolsamide's potential pharmacological effects against SARS Cov-2, comes from the *in vitro* and preclinical studies. The positive results of these investigations

have encouraged the initiation of comprehensive clinical trials of niclosamide formulations for the treatment of COVID-19. Table 1 gives an account of these clinical trials registered in various countries.

Table 1: Registered clinical trials to examine niclosamide's safety and/or efficacy in COVID-19

S. No.	Study title and NCT no.	Phase	Interventions	Dose	Route of administration	Trial status	Country
1	Niclosamide for Mild to Moderate COVID-19 NCT04399356	2	Drug: Niclosamide Other: Placebo	2 gm per day	Oral	Completed	United States
2	Effectiveness of Niclosamide as Add-on Therapy to the Standard of Care Measures in COVID-19 Management NCT04753619	2	Drug: Niclosamide oral Tablets	first day 4 gm/d then on the second day 3 gm/d	Oral	Recruiting	Iraq
3	A Study to Evaluate the Efficacy and Safety of a Novel Niclosamide Suspension Formulation For COVID-19 (NICLONEX) NCT04558021	3	Drug: Niclosamide suspension Other: Placebo	200 mg/10 ml 3 times a day	Oral	Recruiting	Turkey
4	Safety and Efficacy of Niclosamide in Patients With COVID-19 With Gastrointestinal Infection (RESERVOIR) NCT04858425	2	Drug: Niclosamide Drug: Placebo	400 mg 3 times daily	Oral	Active, not recruiting	United States
5	Study of Niclosamide in Moderate and Severe Hospitalized Coronavirus-19 (COVID-19) Patients NCT04603924	2 and 3	Drug: Niclosamide Drug: Placebo	1,000 mg twice a day	Oral	Recruiting	United States
6	To Assess the Safety, Tolerability and Pharmacokinetic Properties of Niclosamide Injectable (DWRX2003) for the Treatment of COVID-19 in Healthy Volunteers NCT04749173	1	Drug: DWRX2003, 96 mg Drug: DWRX2003, 432 mg Drug: DWRX2003, 144 mg	96 mg 432 mg 144 mg	Intramuscular	Completed	Korea
7	Randomized-controlled Trial of the Effectiveness of COVID-19 Early Treatment in Community NCT05087381	4	Drug: FluvoxaMINE Maleate 50 MG Combination Product: Fluvoxamine, Bromhexine Combination Product: Fluvoxamine, Cyproheptadine Drug: Niclosamide, Pill Combination Product: Niclosamide, Bromhexine	50 mg, 1 tablet in the morning and 50 mg 2 tablets before bedtime	Oral	Completed	Thailand
8	Prophylaxis for patients at Risk of COVID-19 infection-V (PROTECT-V) NCT04870333	2 and 3	Drug: Niclosamide Drug: Placebo Drug: Ciclesonide Drug: Sotrovimab	5.6 mg	intranasal	Recruiting	United Kingdom
9	Safety of Ascending Doses of Niclosamide (UNI911 INHALATION) in Healthy Volunteers NCT04576312	1	Drug: UNI911 inhalation 1% and intranasal spray 1% Drug: Placebo	(2 x 150 µl, 1% ~ 2.5 mg) (6 ml 1% ~ 50,4 mg)	Intranasal Inhalation	Completed	Denmark
10	To Evaluate the Safety, Tolerability and Pharmacokinetic Properties of DWRX2003(Niclosamide Injectable) NCT04592835	1	Drug: DWRX2003	288 mg 576 mg 960 mg	Intra-muscular	Not yet recruiting	-
11	Clinical Trials to Assess Safety and Efficacy of DWRX2003 Combination with Remdesivir in Moderate to Severe COVID-19 Patients NCT05226533	2	Drug: DWRX2003 Drug: Placebo	432 mg 960 mg	Intramuscular	Not yet recruiting	-
12	Safety and Pharmacokinetics of a Novel Niclosamide Solution in Combination With camostat (NIC-002) NCT04644705	1	Drug: Niclosamide Drug: Placebo Camostat	1600 mg once daily 2000 mg once daily 500 mg three times	Oral solution chewing tablets oral solution and chewing tablets	Completed	Germany
13	To Evaluate Safety, Tolerability, Pharmacodynamics, and Pharmacokinetics of DWRX2003 Against COVID-19 NCT04524052	1	Drug: DWRX2003 Drug: Placebo	144 mg 432 mg 960 mg	Intramuscular	Not yet recruiting	-

Phase 1 clinical study of niclosamide formulation for inhalation and intranasal application (UNI91104) was conducted in Denmark (NCT04576312) between 29 June 2020 and 08 August 2020. No serious adverse events were observed among 34 healthy subjects receiving UNI91104. Mild irritation in the upper respiratory tract following inhalation was the most noted frequent adverse event. (45 events in 26 healthy volunteers, 59% of all healthy volunteers). Nasal application of the formulation was well-tolerated. There was no significant difference in pulmonary function of the treatment and placebo groups. Niclosamide showed linear pharmacokinetics. Thus, overall outcome of the phase 1 trial was encouraging in terms of safety and tolerability. In another randomized, placebo-controlled trial, niclosamide efficacy in reducing SARS-CoV-2 shedding and duration of symptoms among patients with mild to moderate COVID-19 was investigated. Mean time to oropharyngeal viral clearance and symptom resolution was calculated for test and placebo groups. However, no statistically significant difference was observed between the groups. The reports of the other ongoing and completed trials will be able to throw light on the clinical efficacy of niclosamide in the treatment of COVID 19 infection.

Future directions

COVID-19 has created a politically, financially, and emotionally difficult scenario throughout the world. Its first and second waves were extremely deadly, infecting over 184 million people and killing 3.98 million people globally. The third wave though milder in terms of mortality rate, infected the number of people. There is a continued threat of this viral infection coming up in the future with unpredictable severity. Instead of developing new drugs, drug repurposing is an emerging method in which an existing, failed, abandoned, or clinically established drug is reintroduced for a new activity in a shorter period of time. Niclosamide is one such anthelmintic drug that has shown promising anti SARS-CoV-2 activity. There have been a number of attempts to overcome the challenge of poor solubility and bioavailability of niclosamide through developing various formulations. Also, various routes of administration such as oral, parenteral and pulmonary have been explored to efficiently treat the COVID-19 infection. However, more extensive efforts are desired to deliver the drug mainly to respiratory tract to tackle the infection effectively and locally. Hence, Some of these formulations have now being tested in clinical trials throughout the world. Few of the completed trials have confirmed the safety of the formulations but reports are yet awaited for the confirmatory evidences of their efficacy. The outcomes of the clinical studies would decide the fate of niclosamide as an effective treatment or a part of treatment protocol against the COVID-19 viral infection.

CONCLUSION

Repurposing of existing drugs for other indications is an effective way of expanding the therapeutics in a fast-track manner. Niclosamide is one such age-old anthelmintic drug that has shown potential pharmacological activities during *in vitro* and preclinical studies. One such significant indication is its anti-COVID-19 activity. The outcomes of the ongoing clinical studies will mark the success of niclosamide as a safe and efficacious treatment option for the COVID-19 infections.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

Declared none

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