



# Nitazoxanide and COVID-19: A review

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## Abstract

Coronavirus disease 2019 (COVID-19) is a current global illness triggered by severe acute respiratory coronavirus 2 (SARS-CoV-2) leading to acute viral pneumonia, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), and cytokine storm in severe cases. In the COVID-19 era, different unexpected old drugs are repurposed to find out effective and cheap therapies against SARS-CoV-2. One of these elected drugs is nitazoxanide (NTZ) which is an anti-parasitic drug with potent antiviral activity. It is effectively used in the treatment of protozoa and various types of helminths in addition to various viral infections. Thus, we aimed to elucidate the probable effect of NTZ on SARS-CoV-2 infections. Findings of the present study illustrated that NTZ can reduce SARS-CoV-2-induced inflammatory reactions through activation of interferon (IFN), restoration of innate immunity, inhibition of the release of pro-inflammatory cytokines, suppression of the mammalian target of rapamycin (mTOR), and induction of autophagic cell death. Moreover, it can inhibit the induction of oxidative stress which causes cytokine storm and is associated with ALI, ARDS, and multi-organ damage (MOD). This study concluded that NTZ has important anti-inflammatory and immunological properties that may mitigate SARS-CoV-2 infection-induced inflammatory disorders. Despite broad-spectrum antiviral properties of NTZ, the direct anti-SARS-CoV-2 effect was not evident and documented in recent studies. Then, *in silico* and *in vitro* studies in addition to clinical trials and prospective studies are needed to confirm the beneficial impact of NTZ on the pathogenesis of SARS-CoV-2 infection.

**Keywords** Acute lung injury · Acute respiratory distress syndrome · Anti-inflammatory · Antiviral · Oxidative stress · Pro-inflammatory cytokines

## Background

Coronavirus disease 2019 (Covid-19) is a recent worldwide infectious disease triggered by severe acute respiratory coronavirus 2 (SARS-CoV-2). This virus could lead to various consequences including pneumonia, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), and cytokine storm in severe cases. In general, Covid-19 is asymptomatic or presented with mild symptoms in 85% [1].

In the Covid-19 era, different unexpected old drugs are repurposed to find other alternatives with effective and cheap properties against SARS-CoV-2. One of these elected drugs is nitazoxanide (NTZ) which is an anti-parasitic drug with antiviral activity. It was effectively used in the treatment of protozoa and various types of helminths in addition to various viral infections. NTZ is commonly used in the treatment of *Giardia intestinalis* and *Cryptosporidium parvum* and has been reproduced for the management of influenza [2]. As well, NTZ is effective in the management

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of hepatitis B virus (HBV) and has some efficacy against hepatitis C virus (HCV) [3].

## History of NTZ

NTZ is a nitrothiazole benzamide derivative (2-acetyloxy-*N*-5-nitro-2-thiazolyl) (Fig. 1). It was first used in 1975 as an anthelmintic agent against liver trematodes and intestinal cestodes as described by Jean Francois Rossignol [4].

It has been used worldwide mainly in Latin America as an anthelmintic drug since 1996. In 2002, Food and Drug Administration (FDA) approved NTZ as a therapy for diarrhea caused by *Cryptosporidium* species and *G. intestinalis* in children, and in 2004 for *G. intestinalis* in adults [4]. NTZ is also effective against anaerobic bacteria mainly *Helicobacter pylori*, *Bacteroids*, and *Clostridium* species [5]. The main mechanism of NTZ against anaerobic bacteria and protozoa is through inhibition of the pyruvate-ferredoxin oxidoreductase (PFOR) enzyme, which is necessary for anaerobic energy metabolism, however, its main antiprotozoal mechanism of action is unknown [5].

## Dosage forms and pharmacokinetic properties of NTZ

NTZ may be administered as an oral suspension (100 mg/5 mL) or tablet (500 mg), which are used twice daily for three consecutive days only. Absorption of NTZ is

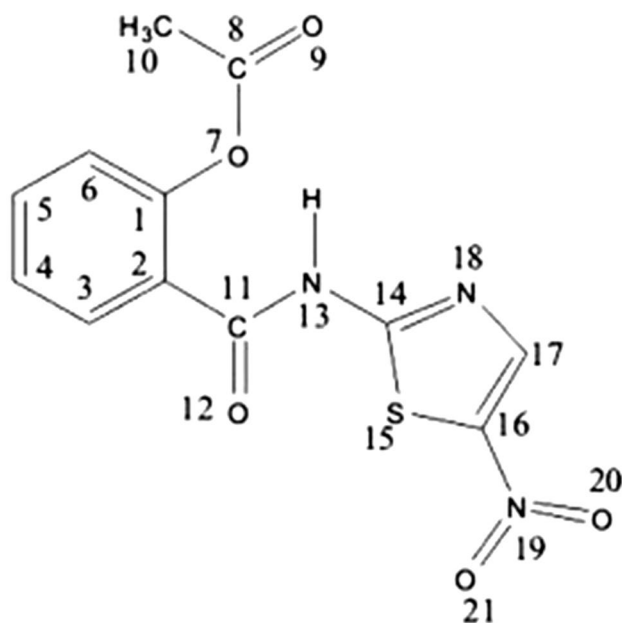


Fig. 1 The chemical structure of NTZ

enhanced by food, 25% of the absorbed oral dose is excreted in urine and 75% by the bile [6]. Plasma concentration of NTZ following oral absorption is 2 mg/L within 2–4 h and its urinary elimination time is about 7.3 h. NTZ is characterized by high plasma protein binding (> 99%), and it is metabolized in plasma by the action of plasma esterase to form des-acetyl derivatives (des-acetyl-nitazoxanide) like tizoxanide (TTZ) which is also active [7]. TTZ then undergoes conjugation, primarily by glucuronidation to form tizoxanide glucuronide which is the major human metabolite of NTZ and it is known to retain some activity in its own right [8] as shown in Fig. S1. Different in vitro studies showed that NTZ and TTZ has no inhibitory effect on the cytochrome P450, therefore it is expected that no important drug interactions would occur when NTZ is co-administrated with other drugs [7].

## Antiviral effects of NTZ

Different investigations and laboratory studies disclosed that NTZ has broad-spectrum antiviral activity, so remarkable efforts tried to apply this effect in clinical practice. Consequently, new pharmaceutical preparations of controlled-released NTZ to deliver this drug are developed. It has been shown that NTZ and its active metabolite TTZ inhibit the replication of 16 strains of influenza H1N1 and one strain of influenza B [9]. A previous study [10] illustrated that NTZ synergized the effect of oseltamivir against influenza A H1N1 and avian A H5N9. The anti-influenza mechanism of NTZ is through inhibition of the maturation of viral hemagglutinin at the post-translational step. However, NTZ had no effects on viral neuraminidase, M2 protein, viral entry, viral adsorption, and infectivity [11]. Moreover, NTZ potentiates the production of interferon-alpha (IFN- $\alpha$ ) and beta from the fibroblasts, which also have inhibitory effects on the maturation of influenza H1N1 [12].

NTZ is also effective against norovirus and rotavirus that can cause viral gastroenteritis. It was illustrated that NTZ alone or in combination with ribavirin represents an effective promising therapeutic modality against norovirus gastroenteritis mainly in immunocompromised patients [13].

Different clinical trials and studies revealed that NTZ is efficient against HBV and HCV infections. A clinical trial involving 12 adults having chronic HBV treated by NTZ for one year showed that eight patients became HBV-Ag negative and four patients were still HBV-Ag positive. Then, within three months, three of the four HBV-Ag positive patients became HBV-Ag negative [3]. Similarly, Nikolova et al. [14] reported that NTZ is considered a potential alternative drug alone or when added to the standard protocol for the management of chronic HCV. NTZ inhibits HCV through activation of protein kinase which is important

for innate immune response. Moreover, it can attenuate the HCV-induced cytopathic effect and disrupt the viral structural proteins via depletion of the intracellular  $\text{Ca}^{2+}$  store in the endoplasmic reticulum [15]. In addition, NTZ can suppress the replication of *Flaviviridae* viruses such as *dengue* virus, yellow fever virus, and Japanese encephalitis virus via inhibition of the viral adsorption and entry. Of interest, NTZ may synergize with drugs that are used against human immune deficiency virus (HIV), mainly reverse transcriptase and integrase inhibitors. It may reduce the infectivity of HIV through attenuation of the viral entry and reverse transcription [11].

### Antiviral effects of NTZ analogs

Moreover, because of the possible biological properties, structurally adapted NTZ-based analogs or structurally connected molecules were synthesized and investigated for their biological activity. Besides, recently synthesized analogs of NTZ seemingly have protuberant antiviral activity even in some cases better than the parent drug NTZ itself [16]. Though NTZ and some of its analogs were examined for a wide variety of biological activities, heteroaryl amide analogs were not screened for several bioactivities. Furthermore, NTZ-based analogs might be effective as antiviral agents against SARS-CoV-2 and, therefore, the synthesis of new series of molecules could be effective in the management of COVID-19 [17]. As well, second-generation nitazoxanide derivatives: thiazolides are effective inhibitors of the influenza A virus. Thiazolides are the most common derivatives of NTZ, the mode of action of the thiazolides is under ongoing investigation, but there is no evidence that they are acting directly against viral RNA or protein. In the case of influenza A, it has been shown that thiazolides act at a post-translational level after entry into the cell, between the endoplasmic reticulum and the Golgi apparatus, preventing the maturation of the viral hemagglutinin [18]. Intracellular transport and insertion into the host plasma membrane are thereby both impaired. Since thiazolides are selectively acting on hemagglutinin without targeting neuraminidase, it might be expected that they would retain good activity against influenza A virus strains resistant to amantadine or oseltamivir. Certainly, both in vitro and clinical trials referred to a good synergy between nitazoxanide and oseltamivir is observed, and the lack of direct action against viral RNA or protein should lessen the development of resistance. In support of this, we note that in the case of hepatitis C as well as IAV (PR8 strain) it was shown that generation of resistant strains was not observed following challenge with nitazoxanide; indeed, susceptibility toward other directly acting antivirals was unaffected.

These results are consistent with a cell-mediated, not virus-mediated, effect of NTZ [19].

### NTZ and COVID-19

Coronaviruses (CoVs) are enveloped, positive-sense single-strand RNA viruses, and characterized by a large genomic size ranging from 27 to 34 kb. CoVs triggering mild human respiratory tract infections include HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1 [20, 21]. However, highly pathogenic beta-CoVs including SARS-CoV and the Middle East Respiratory Syndrome CoV (MERS-CoV) led to pandemic and epidemic serious diseases [11, 22]. Various studies reported that NTZ could inhibit the replication of canine CoV-S378, bovine CoV, murine CoV, and human enteric CoV. Both NTZ and its active metabolite inhibit MERS-CoV cultured in LLC-MK2 cells [23, 24].

SARS-CoV-2 has a genomic similarity with MERS-CoV in about 50% and with SARS-CoV in about 79%. However, SARS-CoV-2 has lower pathogenicity but with higher transmissibility rate compared with SARS-CoV [25, 26]. Therefore, drugs that were effectively used in the control of both SARS-CoV and MERS-CoV like NTZ might be effective as a therapeutic approach for COVID-19 [27].

In COVID-19, SARS-CoV-2 binds to the highly expressing angiotensin-converting enzyme 2 (ACE2) receptors on certain cells such as pulmonary alveolar type II pneumocytes, endothelial cells, and lung macrophages (Al-Kuraishy et al., 2021). The binding of SARS-CoV-2 to the ACE2 receptors is facilitated by the host cellular trans-membrane protein serine 2 (TMPRSS2) via trimming of SARS-CoV-2 spike protein (SP) [28]. Entry of SARS-CoV-2 into the affected cells induces cytopathogenic effects and immunological reactions with subsequent induction of pyroptosis and release of damage-associated molecular patterns (DAMPs) [29]. This process is detected by specific toll-like receptors (TLR) 7 and 8 on the nod-like receptor pyrin 3 (NLRP3) inflammasomes which acts as RNA sensor. Activation of cellular NLRP3 inflammasomes stimulates the release of nuclear factor kappa B (NF- $\kappa$ B), which triggers alveolar macrophages for the production and discharge of pro-inflammatory cytokines as interleukins (IL-6 and IL-8), macrophage inflammatory protein-1 alpha (MIP-1 $\alpha$ ), and tumor necrosis factor-alpha (TNF- $\alpha$ ) [30]. These pro-inflammatory cytokines activate the immune cells such as monocytes, macrophages, and activated T cells for the elimination of SARS-CoV-2 (Al-Kuraishy et al., 2021). This process is controlled by type I interferon (IFN) response to diminishing the viral replication and the cytopathic effect in the early phase of COVID-19 [31]. Nevertheless, down-regulation of type I IFN by SARS-CoV-2 leads to immunological escape with overproduction

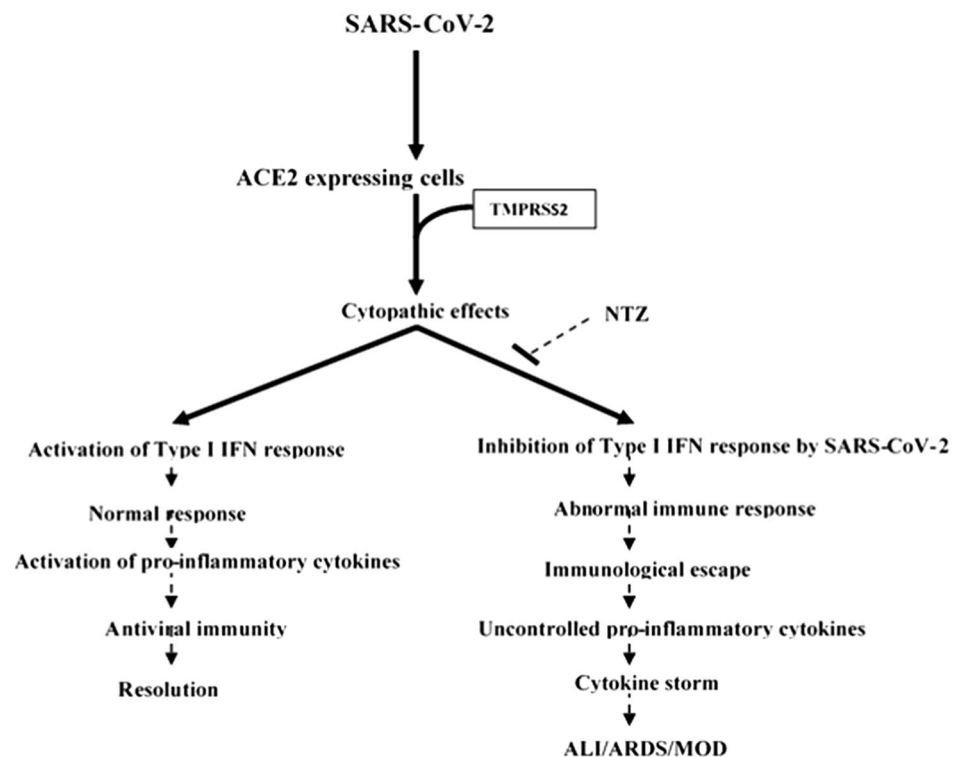
of pro-inflammatory cytokines and abnormal immune response [32]. This unbalanced immune response triggers the synthesis and discharge of the pro-inflammatory cytokines and induction of cytokine storm-induced ALI, ARDS, and MOD [33] (Fig. 2).

NTZ prevents SARS-CoV-2-induced IFN down-regulation; thereby it suppresses the immunological escape and development of cytokine storm. Precisely, non-structural protein-1 (NP1) of SARS-CoV-2, inhibits mRNA of IFN- $\beta$ , while NP15 and N proteins block the IFN pathway. In this concern, NTZ prevents SARS-CoV-2-induced IFN reduction with the activation the endogenous IFN synthesis and release [13] IFN pathway is necessary in the prevention of different viral infections, mainly in the case of SARS-CoV. It was stated that SARS-CoV with defective NP15 did not affect host-innate immunity, while SARS-CoV with competent NP15 leads to lethal immunological reactions due to reduction of IFN in mice [13, 34]. SARS-CoV NP15 has a 90% similarity with that of SARS-CoV-2, therefore inhibition of SARS-CoV-2 NP15 by antiviral agents or attenuation of its inhibitory effect on the IFN pathway by the action of NTZ might be an advantageous modality in the control of COVID-19 [34]. NTZ may cause severe reduction in case of SARS-CoV-2 infection through intensification of IFN pathway, augmentation of cytoplasmic RNA sensing, depleting of ATP-sensitive  $Ca^{2+}$  store, phosphorylation of protein kinase, inhibition of cellular translation, and impairment of viral replications [35].

Similarly, NTZ can reduce the inflammatory burden and development of cytokine storm during SARS-CoV-2. This could be attained via inhibition of the pro-inflammatory cytokines like IL-1 $\beta$ , IL-6, IL-13, and TNF- $\alpha$  with activation of the anti-inflammatory cytokines like IL-10 [36]. Miner et al. [37] illustrated that NTZ has an important effect in the management of various respiratory illnesses such as asthma and other chronic obstructive pulmonary diseases. They stated that NTZ can inhibit  $Ca^{2+}$  activated  $Cl^-$  channel (TMEM16A); therefore, NTZ may prevent SARS-CoV-2-induced bronchoconstriction and other respiratory complications. Cadegiani et al. [38] experimental study illustrated that NTZ derivatives attenuate ALI via inhibition of the discharge of the pro-inflammatory cytokines and oxidative stress. Thus, NTZ might be an effective drug in the management and prevention of SARS-CoV-2-induced ALI similar to that of chloroquine and ivermectin [38]. Thus, the combination of NTZ and hydroxychloroquine is used in managing COVID-19 to overcome SARS-CoV-2-induced deregulation of the innate immune system [39]. Besides, restoration of the activity of the innate immune system is achieved in COVID-19 cases through using a combination of NTZ and azithromycin [40].

Taken together, NTZ alone or in combination with other immunomodulating agents may affect the COVID-19 course through up-regulation of the immune response, down-regulation of SARS-CoV-2-induced immune dysfunction,

**Fig. 2** Abnormal and normal immune response in SARS-CoV-2 infection. The binding of SARS-CoV-2 to ACE2 expressing cells is facilitated by cellular TMPRSS2. SARS-CoV-2 leads to cytopathic effects which are mitigated through activation of type I IFN immune response leading to resolution. However, inhibition of type I IFN immune response by SARS-CoV-2 leads to immunological escape with the development of ALI, ARDS, and MOD. NTZ blocks the inhibitory effect of SARS-CoV-2 on the type I IFN response



and attenuation of cytokine storm-induced ALI and ARDS [16, 40].

NTZ has a large safety profile in a dose-dependent manner and it is marginally safe in pregnancy (category B). Therefore, NTZ therapy was elucidated for managing COVID-19 in pregnant women in Mexico. A prospective study in Mexico involved 20 hospitalized pregnant women with COVID-19 treated with NTZ 600 mg for five days and illustrated that NTZ is effective in the control of COVID-19 pneumonia [41]. In the bargain, Rocco et al. [42] a randomized and placebo-controlled trial involving 392 patients suffering from mild symptoms of COVID-19, of these 198 were treated by placebo and 194 were treated with NTZ 500 mg/day for five consecutive days. Following the five days, the viral load was reduced significantly in the NTZ-treated group only when compared to the placebo. However, the secondary outcomes weren't significantly different, suggesting that NTZ is effective against COVID-19 pneumonia but doesn't accelerate the resolution. Besides, a randomized clinical trial was done in December 2020 to illustrate the effect of hydroxychloroquine alone or in combination with NTZ on the outcomes of the mechanical ventilation in the severe illness of COVID-19 [43].

## Immunological effects of NTZ in COVID-19

NTZ in addition to its modulator effect on the IFN pathway, is regarded as a potent autophagy activator. It has been reported that autophagy activators, like ivermectin, have an important role in inducing the cytoplasmic degradation of SARS-CoV-2 infected cells [44]. Induction of autophagic cell death is beneficial in regulating and controlling the duration and level of inflammation. As the necrotic cells are regarded as potent activators of the inflammatory response in the neighbored immune cells, thus, removal of the necrotic cells as part of the autophagic function may prevent the inflammatory reaction and inhibit the discharge of the pro-inflammatory cytokines [45]. Hence, induction of autophagic death by NTZ might be behind its beneficial impact in COVID-19.

Of note, both mitogen-activated protein kinase (MAPK) and NF- $\kappa$ B are activated by SARS-CoV-2 proteins causing a trigger of the pro-inflammatory cytokines and inflammatory burst [46]. Shou et al. [47] illustrated that NTZ is regarded as a potent inhibitor of MAPK and NF- $\kappa$ B signaling pathways; thereby it may mitigate the inflammatory reactions in COVID-19.

In addition, the mammalian target of rapamycin (mTOR) is activated by SARS-CoV-2 infection causing severe inflammation in the lung and facilitating the binding of SARS-CoV-2 to the ACE2 with progress to lung lymphangioleiomyomatosis [48]. As well, the mTOR

pathway is regarded as a negative regulator of the cell autophagy which might enhance the viral infection-induced inflammatory reactions [49]. Lam et al. [50] illustrated that NTZ inhibits autophagy through suppression of mTOR, thereby NTZ might have a potential effect on mitigation of SARS-CoV-2 pathogenesis and its associated inflammatory illnesses. Furthermore, NTZ has also shown noteworthy immunomodulation activities, inhibiting macrophages activity and production of pro-inflammatory cytokines [51]. Different recent studies recognized that macrophage activation syndrome and the high pro-inflammatory cytokines may be driven by SARS-CoV-2 infection causing the progress to ALI and ARDS [52].

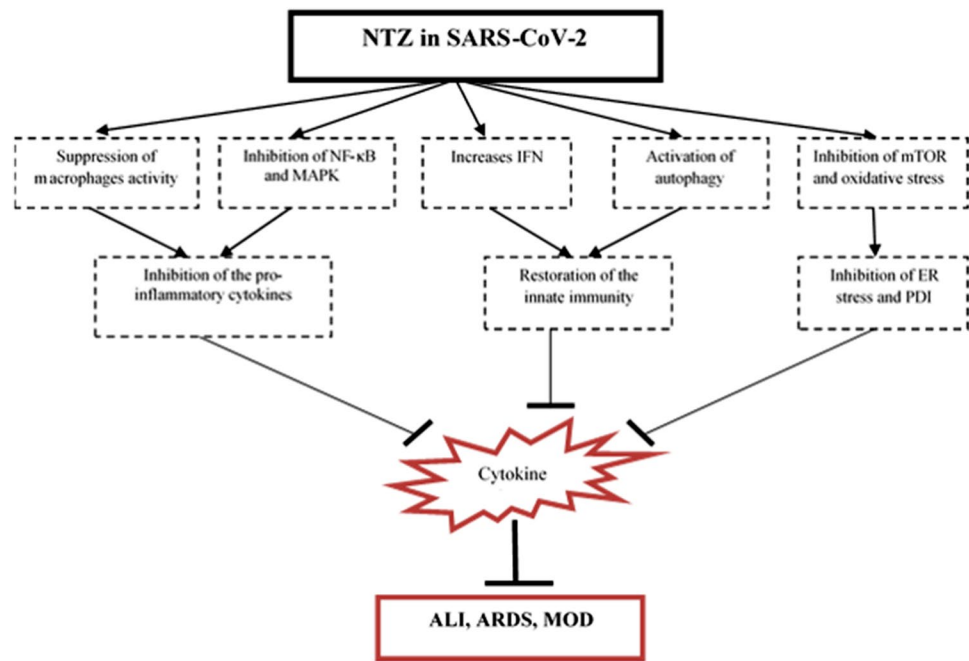
On the other hand, IL-6 is regarded as a potential predictor of severity of COVID-19 and is often correlated with ALI and ARDS [53]. NTZ may reduce the severity of COVID-19 via inhibition of IL-6 [54]. The mechanism of this inhibition is unidentified and believed to be through the suppression of autophagy [55].

In addition, SARS-CoV-2 infection induces direct oxidative stress injury due to acute infection or indirectly through augmentation of Ang II level and reduction of Ang 1–7 levels [56]. It is well-known that Ang II is regarded as nicotinamide adenine dinucleotide phosphate (NADPH) enhancer while Ang1-7 is NADPH inhibitor [57]. Besides, the high oxidative stress that is usually occurring in case of SARS-CoV-2 infection is related to the activity of protein disulfide isomerase (PDI) which is an important regulator of oxidative stress. So, the reduction of PDI is accompanying an increased COVID-19 severity [58]. It has been shown that NTZ has a significant antioxidant effect and it can reduce endothelial dysfunction and the endoplasmic reticulum (ER) stress [59]. Thereby, it may reduce the oxidative stress brought by SARS-CoV-2 infection. The net effects of NTZ on the inflammatory process and the immunological profile in patients suffering from COVID-19 are summarized in (Fig. 3).

Taken together, in virtue of its anti-inflammatory, antioxidant, and inhibition of inflammatory signaling pathways, NTZ inhibits the propagation of immunoinflammatory disorders in patients with SARS-CoV-2 infection. The direct anti-SARS-CoV-2 effect of NTZ was not confirmed, though a recent study revealed that NTZ may interfere with *N*-glycosylation of SARS-CoV-2 spike protein [60]. Likewise, Riccio et al. [61] observed that NTZ blocks the maturation of SARS-CoV-2 spike protein and fusion activity with ACE2 with an effect independent of emergence spike variants (Riccio et al., 2022). Therefore, NTZ might be an effective agent used in the prophylaxis and treatment of mild to severe SARS-CoV-2 infection including the variant strains.

The present study had several limitations including; limitations of the molecular and immunological studies that

**Fig. 3** Potential effects of NTZ on COVID-19. NTZ inhibits the macrophages activity, production of the pro-inflammatory cytokines, MAPK, and NF- $\kappa$ B. All of these factors are stimulated in SARS-CoV-2 infection. NTZ activates IFN and autophagy leading to the restoration of innate immunity. As well, NTZ inhibits both mTOR and oxidative stress leading to the inhibition of endoplasmic (ER) stress and PDI. These effects of NTZ attenuate the progress of cytokine storm and development of ALI, ARDS, and MOD. Activation (✓), inhibition (✗)



confirm the potential role of NTZ. Therefore, *in silico* and *in vitro* studies as well as, clinical trials and prospective studies are recommended for evaluating the effect of NTZ on the pathogenesis of SARS-CoV-2 infection.

## Conclusion

NTZ has important anti-inflammatory and immunological properties that could mitigate the complications induced by SARS-CoV-2 infection. Despite the broad-spectrum antiviral properties of NTZ, the direct anti-SARS-CoV-2 effect was not evident and documented in the recent studies. Therefore, more future studies are needed to evaluate the beneficial outcomes of NTZ in COVID-19.

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**Data availability** All data are available in the manuscript.

## Declarations

**Conflict of interest** The authors have no relevant financial or non-financial interests to disclose.

**Ethical approval** Not applicable

**Consent to participate** Not applicable

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