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Review article

Evaluating NSAIDs in SARS-CoV-2: Immunomodulatory mechanisms and future therapeutic strategies

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A B S T R A C T

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely recognized for their analgesic and anti-inflammatory properties. Amidst the SARS-CoV-2 pandemic, the role of NSAIDs in modulating viral and bacterial infections has become a critical area of research, sparking debates and necessitating a thorough review. This review examines the multifaceted interactions between NSAIDs, immune responses, and infections. Focusing on the immunomodulatory mechanisms of NSAIDs in SARS-CoV-2 and their implications for other viral and bacterial infections, we aim to provide clarity and direction for future therapeutic strategies. NSAIDs demonstrate a dual role in infectious diseases. They reduce inflammation by decreasing neutrophil recruitment and cytokine release, yet potentially compromise antiviral defense mechanisms. They also modulate cytokine storms in SARS-CoV-2 and exhibit the potential to enhance anti-tumor immunity by inhibiting tumor-induced COX-2/PGE2 signaling. Specific NSAIDs have shown efficacy in inhibiting viral replication. The review highlights NSAIDs' synergy with other medications, like COX inhibitors and immunotherapy agents, in augmenting therapeutic effects. Notably, the World Health Organization's analysis found no substantial link between NSAIDs and the worsening of viral respiratory infections. The findings underscore NSAIDs' complex role in infection management. Understanding these interactions is crucial for optimizing therapeutic approaches in current and future pandemics. However, their dual nature warrants cautious application, particularly in vulnerable populations. NSAIDs present a paradoxical impact on immune responses in viral and bacterial infections. While offering potential benefits, their usage in infectious diseases, especially SARS-CoV-2, demands a nuanced understanding to balance therapeutic advantages against possible adverse effects.

1. Introduction

Multiple public health authorities have expressed concerns regarding the utilization of NSAIDs as a therapeutic approach for managing the symptoms associated with coronavirus disease 19 (COVID-19) [1]. On 14th March 2020, the French Health Minister, via Twitter, highlighted the potential of NSAIDs to augment the susceptibility to COVID-19 infection and exacerbate the disease's progression. Specifically, it was hypothesized that Ibuprofen, an easily accessible over-the-counter NSAID, might amplify the viral activities of COVID-19 due to its influence on the upregulation of angiotensin-converting enzyme 2 (ACE-2) expression. The National Health Service recommended substituting NSAIDs with paracetamol (acetaminophen) for the treatment of COVID-19 symptoms, despite the absence of robust evidence regarding the impact of NSAIDs on the enhancement of COVID-19 pathogenesis [2]. Furthermore, inconclusive evidence has suggested that NSAIDs can escalate complications in cases of uncomplicated acute respiratory infections and impede recovery from pneumonia resulting from SARS-CoV infection [3].

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NSAIDs are effective analgesics for inflammatory diseases and are part of the World Health Organization (WHO) pain ladder, with opioid-sparing properties supported by randomized trials [4]. Initial concerns were raised about NSAID use and increased severity of COVID-19, but recent studies in diverse populations show that there are no associations between the use of NSAIDs and increased hospital admissions or worsening outcomes in COVID-19 patients [5–7]. In support of this, a study examining over 2 million patients concluded that there is no evidence of an elevated risk of COVID-19 among individuals who regularly use NSAIDs. Adding on, community data has also shown, that COVID-19 patients under NSAIDs have no increased risk of hospitalization. Limited data on hospitalized patients also suggested no poorer outcomes with NSAID use [8].

Observational cohort studies consistently affirm that NSAIDs do not heighten the risk of SARS-CoV-2 infection or worsen outcomes in COVID-19 patients, as endorsed by major global public health authorities for analgesic or antipyretic use during the pandemic period. Additionally, a meta-analysis study [2], incorporating data from 2414 patients across three studies, demonstrated no substantial difference in fatality risk between NSAID users and non-users. Emphasizing the lack of evidence supporting concerns about NSAIDs and COVID-19 severity, the study discourages restrictions on NSAID use for managing health conditions during the pandemic. However, the paper acknowledges limitations in establishing causality due to the observational nature of the studies, emphasizing the need for randomized controlled trials for conclusive evidence.

Meanwhile, Bruce et al. [7] and Drake et al. [9] conducted a multicenter observational study across several UK hospitals and found no evidence linking routine NSAID use with increased COVID-19 mortality. Both studies suggest a potential modest benefit of NSAID use in survival but underscores the necessity of further investigation. Addressing European authorities' concerns, the studies highlight complications of NSAID use, like upper gastrointestinal effects, arterial thrombotic events, and acute kidney injury particularly in older individuals, while emphasizing the other strengths: a sizable population, comprehensive specialty data, minimal gaps, and representation across England, Scotland, and Wales, including additional clinical demographics.

The primary mechanism of action for NSAIDs is the inhibition of the cyclooxygenase (COX) enzyme, primarily COX-1 and COX-2, leading to a reduction in the production of prostaglandins (PGs) [1,2,10]. The COX-1 enzyme plays a role in maintaining homeostasis and is evenly expressed in the gastrointestinal linings, and kidneys, it is also involved significantly in platelet aggregation. In contrast, COX-2 is present only during an inflammatory response, resulting in the production of cytokines, mitogens, and prostanoids [11]. Inhibition of the COX-1 enzyme may disrupt its homeostatic functions and potentially lead to side effects such as gastrointestinal ulcers and kidney damage. Therefore, selective COX-2 inhibition is considered more advantageous for combating the inflammatory responses resulting from an infection [12].

Various studies have shown the effectiveness of selectively inhibiting COX-2, where one study has demonstrated a reduction of polymorphonuclear (PMNs) leukocyte recruitment in the lungs of murine models with acute lung injury when treated with selective COX-2 inhibitors [13]. Another study, conducted on mice infected with influenza A virus, has emphasized that the absence of COX-2 is linked to a lower mortality rate. In contrast, mice with COX-1 deletion showed an exacerbation of viral infection [14]. Given the significant role of prostaglandins in response to injuries and inflammation, their production may impact the pathogenesis of COVID-19 infection in various ways, such as influencing the susceptibility to infection through the modulation of ACE-2 expression levels and the presence of cell entry receptors for SARS-CoV-2 [15]. Consequently, this may facilitate the replication of SARS-CoV-2 in host cells and induce immune responses as a result. Thus, it is plausible that NSAIDs have the potential to affect the immune response to SARS-CoV-2 vaccination [16].

The relationship between the susceptibility to COVID-19 infection and the modulation of ACE-2 expression by NSAIDs has been moderately studied throughout the COVID-19 pandemic era. Some studies demonstrated the significant decrease of ACE-2 expression caused by some selective NSAIDs, such as Ibuprofen and Diclofenac, increase the susceptibility to COVID-19 infection [17,18]. However, other studies have observed that NSAIDs, such as Ibuprofen and Meloxicam, do not affect ACE-2 expression. Instead, according to Chen (2020), NSAIDs may influence the production of neutralizing antibodies and inflammatory cytokines, thereby impacting the severity of the infection [1]. Moreover, the renin-angiotensin system (RAAS) also plays a role. Through the implementation of network pharmacology, a research endeavor postulated that the inhibition of associated target proteins within the RAAS by three NSAIDs—Nabumetone, Rofecoxib, and Indomethacin—could potentially ameliorate the heightened inflammation triggered by SARS-CoV-2 [16].

This review extensively explores the influence of NSAIDs on viral and bacterial infections, with a specific focus on SARS-CoV-2. It discusses NSAIDs' impact on viral infections, highlighting their dual role in modulating immune responses and antiviral mechanisms. The manuscript examines NSAIDs' potential effects in augmenting anti-tumor immunity via the COX-2/PGE2 pathway. The interplay between NSAIDs and the p38 MAPK pathway in SARS-CoV-2 is analyzed, alongside mechanisms of COX-2 activation in coronavirus family infections. The roles of ACE-2, RAAS imbalance, and cytokine storms in SARS-CoV-2 are also addressed. The paper concludes with insights into NSAIDs' dual immunomodulatory effects and their nexus with viral infection and metabolic acidosis, underlining the complexity of their usage in SARS-CoV-2.

1.1. The impact of NSAIDs on viral infections

The impact of NSAIDs on SARS-CoV-2 patients has been interpreted differently [1,19]. The role of NSAIDs on viral infections appears to be conflicting. Although NSAIDs exhibit stimulatory effects on interferon, nitric oxide, and T lymphocytes, they also demonstrate inhibitory effects on macrophages, neutrophils, and the formation of antibodies [10]. Another study also suggests that NSAIDs reduce the recruitment of polymorphonuclear neutrophils and cytokine release during inflammation [11], and have been shown to compromise the antiviral activity of interferon-γ (IFN-γ)-induced innate immune cells, simultaneously inhibiting the production of IL-4 by CD4 T cells [20].

Despite these inhibitory effects, studies have shown that NSAIDs can hinder the entry of viruses into cells. At the same time, it impedes the replication of various viruses, as evidenced by the inhibitory effect of naproxen on the replication of SARS-CoV-2 [21]. Certain NSAIDs like indomethacin and celecoxib affect the replication and dissemination of viruses like Vesicular Stomatitis Virus and Sapovirus, primarily through elevating nitric oxide concentration and subsequently suppressing COX enzyme activity [22,23]. In relation, to the cyclooxygenase enzyme, a study involving mice with a COX-2 gene knockout demonstrated suppressed cytokine release upon viral stimulation, whereas mice with the absence of COX-1 had no impact on its interleukin and interferon levels. Notably, mice lacking the COX-2 isoform demonstrated lower mortality rates when infected with the influenza virus [24].

However, an analysis done by the World Health Organization (WHO) on more than 70 papers found little evidence linking NSAIDs used with acute viral respiratory infections caused by COVID-19, SARS, or MERS [25]. Lastly, with the increased use of NSAIDs such as ibuprofen with acetaminophen, it was important to note that repeated exposure to these drugs may potentially induce intestinal immune alterations, especially in infants. These may lead to repeated inhibitions of PG synthesis thus affecting the overall immune responses [26]. The consequences of such immune deviation have not been studied yet.

1.2. The impact of NSAIDs on bacterial infections

Numerous studies have been conducted to explore the potential link between NSAIDs and bacterial infections such as empyema. Some studies suggested that NSAIDs, particularly Ibuprofen, independently contribute to hospital admissions for pleural empyema in children and young adults. However, Voiriot et al. [27] argued that these studies suffer from protopathic bias, as NSAIDs were taken by the participants to alleviate symptoms of underlying community-acquired pneumonia.

In congruence with similar research, two hypotheses were proposed regarding the correlation between NSAID use and the risk of complications in pneumonia patients. The first hypothesis is the temporal hypothesis, which suggests that NSAID consumption may delay the diagnosis of pneumonia, leading to a higher risk of developing pleural empyema and bacteremia. Symptoms such as sore throat and fever, which are indicative of pneumonia, may be treated with NSAIDs as antipyretics and analgesics, unknowingly masking the presence of undiagnosed pneumonia. Consequently, NSAID intake upon hospital admission for pneumonia may indicate a delayed diagnosis of the infection. The second hypothesis is the immunological hypothesis, which posits that NSAIDs impede the acute inflammatory response and resolution in pneumonia. In a normal immune response, the invasion of pathogens in the alveolar spaces triggers the generation of prostaglandins by the COX enzyme, initiating further innate immune responses such as the recruitment of PMNs and the phagocytosis and degranulation of foreign substances. However, NSAIDs inhibit COX enzymes and PG production, potentially limiting the recruitment of PMNs and subsequent anti-inflammatory events. This impaired resolution of inflammation in pneumonia may lead to further complications [28].

In a notable investigation, researchers delved into the exacerbating effects of NSAIDs on infections caused by the bacterium *Clostridioides difficile* (*C. difficile*). Through in vitro experiments and mouse models, the study revealed that indomethacin and aspirin heightened the permeability of epithelial cell barriers and increased inflammatory cell death, particularly in conjunction with *C. difficile* toxins. Interestingly, this impact appeared unrelated to the inhibition of COX enzymes, typically targeted by NSAIDs, instead correlating with off-target effects on mitochondria. These findings emphasize the clinical relevance of NSAIDs in *C. difficile* infection contexts and open avenues for further probing into mitochondrial functions during such infections [29].

In the same context, an investigation was conducted to assess the severity of bacterial infections in patients who had prior exposure to NSAIDs before hospitalization. It noted that septic complications, such as infection spread and the necessity for invasive procedures, frequently arose in patients with prior NSAID exposure, regardless of sepsis or shock severity. This indicates a potential impact of NSAIDs on the severity of bacterial infections. The study observed no difference in NSAID or aspirin use between the two groups. Even when considering acute or chronic drug treatments or excluding aspirin from the analysis, there remained no contrast in NSAID utilization between cases and controls. While the study didn't find a significant association between NSAID exposure and severe sepsis or septic shock, it did reveal that NSAID users experienced a longer median time to receive effective antibiotic therapy compared to non-users. This suggests a potential association between NSAID use and delayed appropriate antibiotic treatment [30].

NSAIDs have an optional prescription status, leading to their frequent use, particularly for symptomatic fever and non-rheumatic pain treatment. In 2019, a comprehensive analysis of pharmacological data indicated that using NSAIDs in these indications, potentially indicative of an underlying infection, heightens the risk of severe bacterial complications, especially in lung infections. Clinical observations by the French Pharmacovigilance Network revealed severe bacterial infections even after short NSAID treatments, even in conjunction with antibiotics. Pharmacoepidemiological studies, some minimizing protopathic bias, consistently confirmed this risk. Experimental in vitro and animal studies bolstered the causal link, highlighting effects beyond delaying infection care, including immunomodulatory effects, impacts on Streptococcus pyogenes infections, and reduced antibiotic efficacy. Thus, in infections, symptomatic NSAID treatment for non-severe symptoms is discouraged, according to this network, due to multiple clinical and scientific arguments supporting an increased risk of severe bacterial complications. Moreover, the availability of a safer drug alternative, paracetamol at recommended doses, further legitimizes this precautionary recommendation. In 2020, this recommendation became particularly pertinent with the emergence of COVID-19, which presents symptoms treatable with NSAIDs, raising concerns about their effects on ACE-2 expression levels [31].

In contrast, another study's findings highlighted COX-1 as the primary active isoform in prostaglandin synthesis during infection. NSAIDs' prophylactic or therapeutic inhibition to COX-1 primes leukocytes for bacterial killing by enhancing phagocytic uptake and reactive oxygen intermediate-mediated killing in a cyclic adenosine monophosphate (cAMP)-dependent manner. NSAIDs additionally enhance bacterial killing in humans, displaying an additive effect when combined with antibiotics. Furthermore, by inhibiting COX, NSAIDs prime the innate immune system to clear penicillin-resistant Streptococcus pneumoniae serotype 19A, a concerning vaccine

escape serotype with increasing prevalence and multi-antibiotic resistance. These findings underscore the significance of lipid mediators in host responses to infection and suggest the potential of PG signaling pathway inhibitors as adjunctive therapies, especially concerning antibiotic resistance [32]. Therefore, NSAIDs exhibited antibacterial activity against *E. coli* causing urinary tract infections, showing synergism when combined with antibiotics, primarily by damaging the bacterial cell membrane [32].

A new trend of research focuses on the antimicrobial properties of NSAIDs amidst rising bacterial resistance. It analyzes various studies that examine NSAIDs' antibacterial activities against different bacterial species. Highlighting the potential mechanisms behind these antimicrobial effects, the paper positions NSAIDs as valuable in offering alternative or adjunctive therapeutic strategies in bacterial infection management, especially in the context of global antibiotic resistance challenges. This aspect elevates NSAIDs beyond their traditional anti-inflammatory and analgesic roles, suggesting a significant potential in antimicrobial therapy [33].

1.3. NSAIDs' mechanism in boosting anti-tumor immunity and immunotherapy through COX-2/PGE2 pathway

In a distinct context, NSAIDs are recognized for their immunomodulatory effects, particularly in bolstering specific aspects of anti-tumor immunity mediated by crucial immune cells, such as dendritic cells, natural killer cells, T effector cells, T regulatory cells, and tumor-associated macrophages (TAMs). This facet of NSAIDs significantly influences diverse facets of anti-tumor immunity, primarily attributed to their ability to impede tumor-induced COX-2/PGE2 signaling. A comprehensive scrutiny of both preclinical and clinical data underscores a predominant immunopotentiation effect that fortifies cancer immunosurveillance and immunity [34].

The expression of COX-2 in cancer cells is closely linked to adverse prognoses, contributing to tumor development, proliferation, and metastasis by generating prostaglandin E2 (PGE2). This PGE2 within the tumor microenvironment leads to immune evasion, impairing responses to immunotherapy. COX-2 inhibitors are proposed to counteract PGE2-induced immunosuppression, potentially augmenting or reversing the efficacy of immune checkpoint inhibitors (ICIs). Clinical trials pairing COX-2 inhibitors with chemotherapy or targeted therapy have yielded limited success; however, their potential lies in synergizing with immunotherapy due to their mechanism of action [35]. Animal studies demonstrate that combining COX inhibitors with anti-PD-1 antibodies induces more profound tumor regression compared to using anti-PD-1 antibodies alone. Factors like COX-2 expression levels, metabolites, and COX-2-driven inflammatory agents stand as promising biomarkers for predicting combination therapy outcomes [36].

The ongoing investigation of COX-2 inhibitors combined with immunotherapy, particularly ICIs, signifies a potential strategy to amplify therapeutic responses in cancer treatment, yet further studies are necessary for patient-specific applications. COX-2 inhibitors, exemplified by celecoxib, exhibit potential synergy with ICIs and chemotherapy by potentially activating the immune system while chemotherapy assumes a supportive role [37].

NSAIDs demonstrate a distinct capacity to regulate the dichotomous effects of TAMs, augment the cytotoxicity mediated by natural killer (NK) cells, and facilitate the proliferation and functionality of $CD4^+$ and $CD8^+$ T lymphocytes within the intricate milieu of the tumor microenvironment. This orchestration effectively reinforces the anti-tumor immune response, showing promise for broader applications in tumor immunotherapy [38].

Furthermore, in the realm of tumor immunotherapy, NSAIDs present significant potential in fulfilling the diverse requirements of various immunotherapeutic strategies. Their synergistic or additive effects, when combined with cancer vaccines, monoclonal antibodies (MAbs), and immunostimulatory cytokines, accentuate their capacity to enhance the efficacy of immunotherapies [26]. Considering these multifaceted effects, NSAIDs emerge as valuable candidates in shaping and optimizing future immunotherapeutic interventions [39].

1.4. NSAIDs, the p38 MAPK pathway, and SARS-CoV-2 interplay

The p38 MAPK pathway assumes a pivotal role in the inflammatory cascade triggered by SARS-CoV-2 infection in COVID-19. Given NSAIDs' recognized capacity to modulate this pathway, there's intrigue surrounding their potential contribution to the management of inflammation associated with COVID-19. Initially, Grimes et al. [40] elucidated the central role of the p38 MAPK pathway in instigating the release of pro-inflammatory cytokines, spotlighting its relevance in acute lung injury and myocardial dysfunction during COVID-19 infection. Moreover, it posits that the amplified inflammatory response in COVID-19 could be attributed to heightened p38 activity consequent to the loss of ACE-2 activity upon SARS-CoV-2 viral entry. Additionally, authors suggest a potential direct upregulation of p38 activity by SARS-CoV-2 to bolster its replication, advocating therapeutic p38 inhibition to mitigate infection, supported by promising findings in a SARS-CoV mouse model.

NSAIDs inhibit p38 MAPK activation in T-cells, particularly following T-cell receptor (TCR) engagement. This inhibition does not affect p38 activation induced by other stimuli like lipopolysaccharide or hydrogen peroxide, indicating a specific effect on TCR-mediated p38 activation. Both nonselective and COX-1-specific NSAIDs inhibit TCR-induced p38 activity, but COX-2-specific inhibitors do not. Interestingly, NSAIDs do not impact the Ca2+/calcineurin pathway, another pathway involved in the TCR activation of p38. A key role was suggested for COX-1 in mediating early events of T-cell activation, highlighting the potential of p38 inhibitors as alternative T-cell immunosuppressants [41].

Building on the pivotal role of the p38 MAPK pathway in the inflammatory cascade triggered by SARS-CoV-2 infection as previously discussed, the inhibition of p38 MAPK by NSAIDs holds significant implications for both SARS-CoV-2 infection and COVID-19 progression. Selective inhibitors targeting p38 MAPK can reduce the expression of pro-inflammatory cytokines, such as IL6, CXCL8, CXCL10, and TNF-α, during SARS-CoV-2 infection. This reduction in cytokines may alleviate virus-induced inflammatory responses.

These inhibitors do not noticeably affect viral replication or the interferon-mediated antiviral response of the lung epithelial barrier. Combining p38 inhibitors with antiviral drugs like Remdesivir and Molnupiravir has a synergistic effect, suggesting a novel approach for COVID-19 treatment [42].

Highlighting existing clinical-stage p38 inhibitors for potential repurposing in COVID-19 trials, notably losmapimod with a favorable safety profile, the study asserts the potential of p38 inhibition in alleviating inflammation, vasoconstriction, thrombosis, and cardiac complications linked to severe COVID-19 infection. However, it underscores the imperative for further preclinical trials to delineate p38 activation's role in SARS-CoV-2 animal models, emphasizing the necessity for comprehensive clinical trials to assess the efficacy and safety of p38 MAPK inhibitors in severe COVID-19 cases [40]. In the same context, Valipour [43] emphasized the potential of blood-brain barrier-penetrating p38 MAPK naturally occurring inhibitors in addressing CNS complications of COVID-19. This was highlighted through the characterization of tanshinone IIA and pinocembrin's therapeutic potential in treating these complications. Their robust CNS penetration capabilities and association with the disrupted p38 MAPK pathway induced by COVID-19 were considered in this context. The mechanism for this pathway was further explained by that IL-1β, more prevalent in severe COVID-19 cases, elevates human transmembrane protease serine 2 (TMPRSS2) expression in lung cells. It triggers the p38 MAPK pathway, activating GATA2, which boosts TMPRSS2 production. Overexpressed TMPRSS2 heightens lung cell vulnerability to SARS-CoV-2, while p38/GATA2 inhibitors reduce this susceptibility [44]. Comparative research on SARS-CoV-2, SARS-CoV-1, and MERS-CoV shows that SARS-CoV-2 regulates modulator genes of the MAPK and NFκB pathways differently. This differential regulation may contribute to the unique pathogenicity of SARS-CoV-2 and provide potential therapeutic targets for treatment [45].

2. Mechanisms of COX-2 activation in coronaviruses family infections and potential therapeutic targets

Coronaviruses, possessing the largest known RNA genome, employ multiple mechanisms rather than relying on a single virulence factor to counteract IFN responses, crucial for their survival, proliferation, and successful transmission to new hosts, given the potent antiviral nature of IFN responses [46]. The activation of COX-2 expression in SARS-CoV-2 viral infection can be elucidated by its similarity to other members of the coronavirus family, such as severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS). Observations in SARS-CoV-infected HEK293T cells revealed that the amplification of the COX-2 promoter and subsequent COX-2 protein production occurs via the ERK/NF-κB pathway, modulated by the calcium-dependent PKC isozyme PKCα activated by an influx of extracellular calcium ions, induced by the virus's spike protein [47]. Additionally, the calcium-independent PI3K/PKCε/JNK/CREB pathway, also stimulated by the spike protein, contributes to the induction of COX-2 expression in parallel with the calcium-dependent pathway. Moreover, the nucleocapsid (N) protein of the SARS-CoV virus plays a significant role in activating COX-2 gene expression. Specifically, the N protein activates the COX-2 promoter and its transcription by directly binding to two regulatory elements: a nuclear factor-kappa B (NF-κB) binding site and a CCAAT/enhancer binding protein (C/EBP) binding site. These interactions result in lung inflammation through multiple COX-2 signaling cascades [48].

RNA helicases RIG-1 play a critical role in identifying double-stranded RNA (dsRNA), a specific Pathogen-Associated Molecular Pattern (PAMP) found in SARS and MERS coronaviruses. Recognition of PAMPs by host-pathogen recognition receptors (PRRs) typically induces upregulation of IFN genes, initiating immune responses [46]. Upon SARS-CoV-2 infection, human lung cancer cell lines; A549 and Calu-3 exhibit a significant increase in PTGS2 (Prostaglandin-Endoperoxide Synthase 2) expression, leading to heightened COX-2 production. Specifically, infected ciliated cells display notably elevated PTGS2 levels compared to uninfected bystander ciliated cells, indicating that SARS-CoV-2 activates COX-2 expression through PTGS2 upregulation in a cell-intrinsic manner [1]. Conversely, liver cancer cell line Huh7.5 cells lacking functional RIG-1 genes do not show significant PTGS2 upregulation upon infection. This absence suggests a potential strategy for inhibiting PTGS2 activation and suppressing COX-2 expression by targeting the RIG-1 gene, potentially mitigating associated inflammation [1,46]. Refer to Fig. 1.

3. The role of ACE-2 and imbalance in the RAAS in SARS-CoV-2 infection and the cytokine storm

The angiotensin-converting enzyme-2 (ACE-2) is utilized by SARS-CoV-2 as a receptor for entering host cells [49]. This interaction is initiated by the binding of the virus's spike protein (S) to ACE-2, leading to cell surface fusion. The fusion process can proceed via two main pathways: endosomal/clathrin-dependent and nonendosomal/clathrin-independent. Activation of the spike protein in these pathways requires cleavage at the S1/S2 site by cellular proteases, notably cathepsin L (CTSL) and human TMPRSS2. This cleavage facilitates the release of the virus's genetic material into the host cells [50,51]. SARS-CoV-2 infection induces various inflammatory responses, including disruption of the RAAS and an imbalance in ACE-2, potentially leading to a cytokine storm. This imbalance, characterized by increased ACE relative to ACE-2 expression, is evidenced in ACE-2 knockout mice with cardiac contractility defects, which improve upon ACE ablation. This RAAS disturbance enhances the signaling of key inflammatory mediators such as NF-κB, COX-2, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and transforming growth factor-β1 (TGF-β1) [52]. NF-κB, which is activated by the virus independently of other type I interferon (IFN–I)-related factors, promotes cytokine production through various mediators, including angiotensin II receptor type-1 (AT1R) and toll-like receptors (TLRs). SARS-CoV-2 infection delays antiviral defenses mediated by IFN-I, resulting in excessive cytokine production [53]. Inhibition of NF-κB reduces SARS-CoV-2 replication in vitro, indicating the virus's reliance on NF-κB for replication [54]. Additionally, TNF receptor-associated factor 6 (TRAF6) is implicated in the immune response to SARS-CoV-2, particularly through TLR signaling pathways crucial for detecting viral infections and initiating immune responses [55]. Refer to Fig. 2 for a visual representation.

ACE-2 is primarily expressed in alveolar epithelial type II cells, but its presence extends to various tissues including the kidney, heart, and small intestine [56]. Research involving ACE-2 knockout mice has revealed that disruption in the RAAS leads to heightened

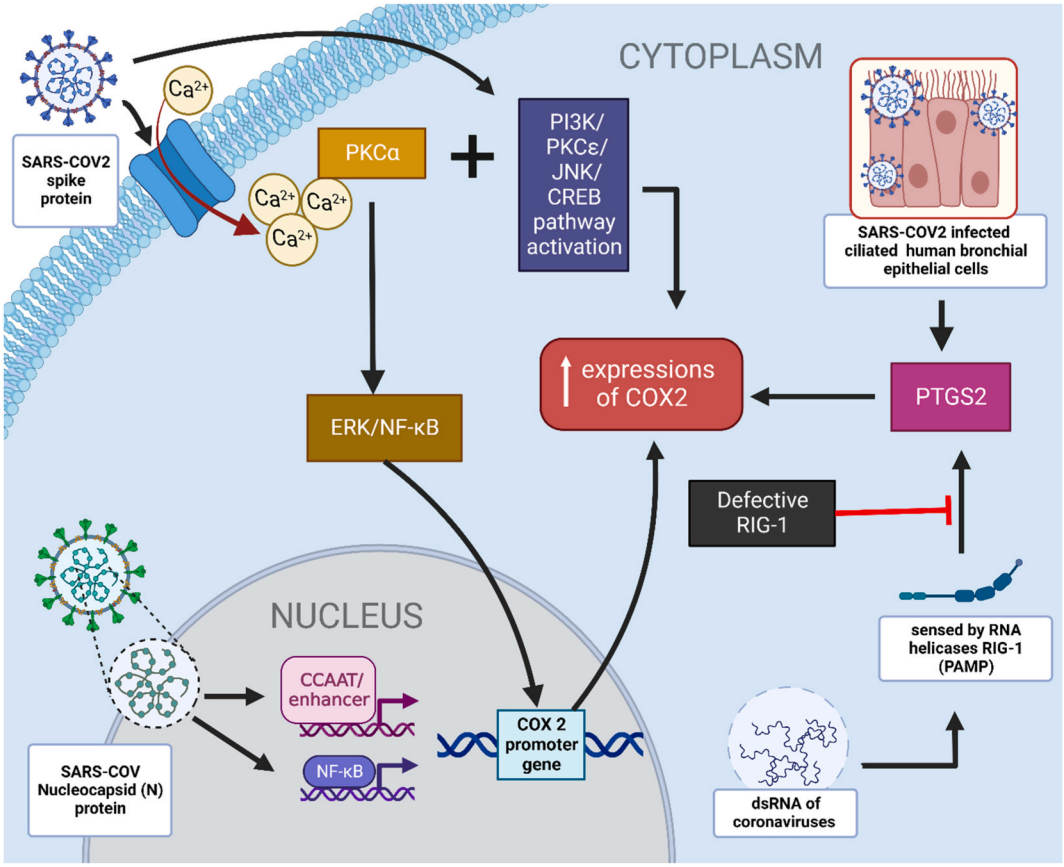


Fig. 1. COX-2 expression pathways induced by SARS-CoV-2.

oxidative stress and an increase in inflammatory cytokines [57]. This effect undermines the protective role of ACE-2 in the cardiovascular system, largely due to its function in converting angiotensin II into the anti-inflammatory and vasodilatory peptide, angiotensin [58]. In contrast, elevated levels of ACE in pleural fluid have been linked to cardiovascular complications, which can be mitigated by ACE inhibitors [59]. In the context of SARS-CoV-2, lung injury is often a consequence of a cytokine storm, initiated by an influx of inflammatory mediators. The virus reduces the surface expression of ACE-2 receptors on infected cells, augmenting proinflammatory angiotensin II levels while diminishing the protective effects of Ang (1–7) [60]. Normally, ACE-2 expression is low in circulation and tissues; however, it is notably upregulated in patients with diabetes, hypertension, and cardiovascular diseases [61]. Furthermore, age and sex have been identified as risk factors: older individuals typically exhibit lower ACE-2 expression than younger counterparts, and women may have reduced susceptibility to cytokine storms, potentially due to higher levels of protective receptors such as AT2 and ACE-2 [62].

4. NSAIDs immunomodulation in SARS-CoV-2 infection

Treatment with NSAIDs typically impacts the production of proinflammatory cytokines, leading to decreased levels of IL-6, IL-17, IL-12, and tumor necrosis factor-alpha (TNF-α) [63]. SARS-CoV-2 infection is marked by elevated production of chemokines, proinflammatory cytokines, and T-cell growth factors, often leading to uncontrolled immune responses in severe COVID-19 cases. This hyperactivation results in widespread and inappropriate immune effector activity. The excessive production of inflammatory cytokines can be traced back to the upregulation of peroxisome proliferator-activated receptor gamma (PPAR-γ) and phospholipase A2 G2D in alveolar macrophages following coronavirus invasion [64]. Clinical studies indicate that patients with high levels of proinflammatory cytokines often experience cytokine release syndrome, characterized by the activation of multiple inflammasome pathways and an accumulation of inflammatory markers. Early immunological interventions that target the blockade of proinflammatory cytokines may thus be beneficial in preventing disease progression and enhancing recovery rates [65]. Meloxicam, specifically, has been noted to reduce certain cytokines like CCL2, CXCL10, IL-2, IL-6, GM-CSF, and TNF-α, which are associated with cytokine storm, although its overall impact on cytokine production is considered minimal [1].

Previous studies have shown that patients with severe COVID-19 infections experiencing tissue hypoxia may develop metabolic acidosis [66]. Acidosis, a common feature in inflammatory conditions, is linked to the activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome, thereby intensifying inflammation [67,68]. The activation of the NLRP3 inflammasome is

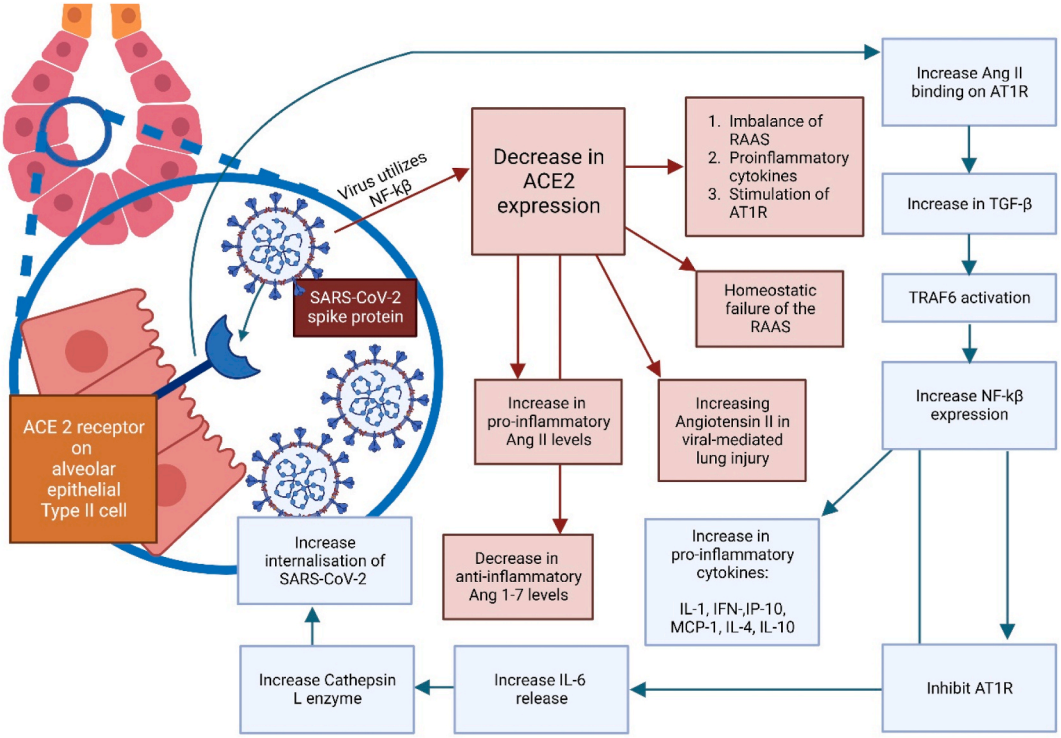


Fig. 2. The effects of SARS COV-2 on pro- and pre-inflammatory mediators mediated by RAAS imbalance and NF-kβ.

controlled by intracellular potassium (K+) ions, and in low K+ environments, acidosis can instigate NLRP3 activation. Notably, the NLRP3 inflammasome can also be triggered by pH-sensitive factors, including the influenza virus M2 protein and the 'Viroporin 3a' viral protein found in SARS coronaviruses [68–70]. Several NSAIDs have been identified as inhibitors of the NLRP3 inflammasome. For instance, Diclofenac may indirectly inhibit NLRP3 activation triggered by coronaviruses through its interaction with acid-sensing ion channels (ASIC) [69]. Both in vitro and in vivo studies have shown that Diclofenac and Mefenamic acid can suppress the activation of the NLRP3 inflammasome and decrease the production of Interleukin-1β (IL-1β) in mouse models of Alzheimer's disease [71].

Upon SARS-CoV-2 infection, an overproduction of neutralizing antibodies occurs, aiming to counteract and eliminate the harmful antigen [72]. In vitro experiments have demonstrated that aspirin, ibuprofen, naproxen, and paracetamol reduce the synthesis of IgM and IgG antibodies in stimulated human peripheral blood mononuclear cells (PBMCs). Of these NSAIDs, ibuprofen notably exhibits the strongest inhibitory effect on antibody synthesis and production, mediated through COX-2 inhibition over varying timeframes and concentrations [73]. In mouse models, spike-specific IgG and IgM antibodies were significantly decreased in those treated with Meloxicam compared to untreated mice. While Meloxicam appears to impair the production of systemic neutralizing antibodies, it does not affect the activation of innate or adaptive immune cells in the lungs [1]. Nevertheless, caution is advised when using NSAIDs, especially in populations vulnerable to immune suppression, such as children, the elderly, and those with compromised immune systems [73]. Intriguingly, Meinberger et al. [74] suggest focusing on biomarkers like C-reactive protein (CRP), interleukin-6 (IL-6), and lactate dehydrogenase (LDH) rather than IgA, IgM, and IgG isotype antibodies, which do not reliably predict the progression of COVID-19. A global epidemiological study investigating the correlation between COVID-19 fatalities and comorbidities on a national level found significant associations with chronic kidney disease and coronary disease. The study confirms the heightened infection risk in individuals aged 65 and older but does not corroborate early assertions by government agencies that certain common comorbidities substantially increase COVID-19 risks [75].

5. NSAIDs' antiviral mechanisms

In the context of SARS-CoV-2, Naproxen has demonstrated similar actions to other NSAIDs in inhibiting viral replication. This is achieved by targeting the coronavirus N protein N-terminal domain (N NTD) and competing with RNA for the binding site. Consequently, Naproxen effectively protects the pulmonary epithelium from viral-induced damage [76]. Additionally, the viral yield of Influenza virus A can be enhanced through the augmentation of its transcription and replication when the nucleoprotein-bound-ribonucleoprotein (NP-RNP) complex is formed. The NP-RNP complex is created when the nucleoprotein (NP) binds to the polymerase of the ribonucleoprotein (RNP) complex. Interestingly, Naproxen has been shown to inhibit the oligomerization of the N protein, targeting the monomeric NP at its RNA binding groove and consequently hindering the formation of the NP-RNA complex. As a result, the transcription and replication of Influenza virus A are inhibited. Various in vitro experiments, such as

fluorescence and surface plasmon resonance, have demonstrated that Naproxen competitively binds to wild-type NP against RNA and prevents the proteolytic cleavage of active nucleoprotein monomers [77].

Naproxen has exhibited similar antiviral effects in SARS-CoV-2-infected VeroE6 cells and reconstituted human primary respiratory epithelium models, as well as in diverse models of influenza A and B and Zika virus [64,76]. Another possible mechanism that was illustrated with naproxen is that it interferes with viral replication by the inhibition of 3C-like protease (3CLpro) [76]. 3CLpro is a significant target for halting the viral synthesis of SARS-CoV-2, as it is primarily responsible for the proteolytic maturation of the virus. An in-silico study by Sisakht et al. [78], suggested that NSAIDs, including celecoxib, meloxicam, and diclofenac, were expected to exhibit antiviral effects in inhibiting 3CLpro with potency comparable to common 3CLpro inhibitors such as Lopinavir and Nelfinavir.

In the context of SARS-CoV-2, viral replication involves the participation of open-reading frame 1a (ORF1a) and ORF1ab coding genes, facilitated by non-structural proteins (nsps) [79]. Among these proteins, the nsp-12-nsp7-nsp8 sub-complex plays a crucial role. This sub-complex includes catalytic subunit 12, which carries out polymerase reactions through its RNA-dependent RNA polymerase (RdRp) activity, with the assistance of nsp7 and nsp8 [80]. These components form the essential core necessary for promoting coronavirus RNA synthesis [81].

Indomethacin has demonstrated the capability to inhibit the nsp7/nsp8 complex by specifically targeting its junction connected to host prostaglandin E synthase 2. This action holds the potential to disrupt the viral lifecycle [64]. Additionally, Indomethacin exhibits inhibitory effects on prostaglandin E synthase 2 and IL-6 expression, suggesting its potential to alleviate the cytokine storm associated with COVID-19 [64]. Furthermore, an in-silico study indicates that diclofenac and Indomethacin are anticipated to display antiviral activity by inhibiting the expression of Peroxisome Proliferator-Activated Receptor (PPAR-γ), potentially mitigating the production of inflammatory cytokines [78]. Considering the potential efficacy of NSAIDs, including Aspirin, Indomethacin, Diclofenac, and Celecoxib, in managing COVID-19-associated coagulopathy, inhibiting SARS viral replication, deactivating the inflammasome, and synergistically inhibiting H5N1 viral infection when used in combination with representative antiviral drugs, these medications present promising prospects as adjunctive therapeutic options in the treatment of COVID-19 [70].

In addition to naproxen, acetaminophen displayed weak binding to the N dimer. In contrast, celecoxib, a COX-2 inhibitor, not only stabilized the dimeric interface but also exhibited tighter binding to the monomeric N protein when compared to naproxen. This suggests a potential correlation between the inhibition of N oligomerization and the inhibition of viral replication. Modeling and Dynamic Light Scattering data indicate that acetaminophen weakly binds to the N dimer without inducing any modification in N oligomerization or demonstrating any antiviral effects.

In vitro studies revealed that COX inhibitors, including ibuprofen and meloxicam, did not impact SARS-CoV-2 entry or replication. Furthermore, it was hypothesized that the proviral effect of celecoxib at low concentrations may be associated with the enhancement of N oligomerization/aggregation, as no clear antiviral effect was observed within its safe concentration range [76]. The effects of NSAID treatment using two commonly prescribed medications, ibuprofen and meloxicam, were investigated for their influence on ACE-2 expression, viral entry, and viral replication in the context of COVID-19. The results indicated that these drugs did not exert any significant influence on ACE-2 expression, viral entry, or viral replication. However, they may potentially affect COVID-19 outcomes by attenuating the inflammatory response and modulating the production of protective antibodies. Recent reports have also suggested that among hospitalized COVID-19 patients, individuals receiving treatment with ibuprofen or naproxen were less likely to require ventilation support [76].

The synergistic effects of various types of medications combined with NSAIDs have demonstrated beneficial outcomes in viral infections [82]. Co-administration of an NSAID with Ketotifen has been assessed and found effective in reducing SARS-CoV-2 viral load. Notably, combinations involving ketotifen and indomethacin, as well as ketotifen and naproxen, exhibited an additive or synergistic effect in reducing the viral yield [83]. In a different context, Celecoxib and Zanamivir, an antiviral drug, have been used in combination therapy to synergistically inhibit CK1, H5N1, and SARS-CoV-2 viral infections. This combination therapy has proven effective in reducing viral load, alleviating acute lung inflammation, and reducing the mortality rate in infected mouse models [70]. Furthermore, when polymerase basic protein 2 (PB2) oligonucleotides were combined with celecoxib and applied to a mouse H5N1 influenza virus infection model, similar positive effects were observed compared to the previous combination, demonstrating significant improvements over the use of PB2 oligonucleotides alone [84].

In the context of mast cell degranulation associated with SARS-CoV-2 infection and its implications in the pathogenesis of COVID-19, a randomized trial on hospitalized COVID-19 cases showed that celecoxib effectively reduced systemic PGE2 levels, mitigated clinical deterioration, and rapidly improved pulmonary CT-chest scans. Additionally, combined adjuvant therapy consisting of oral celecoxib and high-dose famotidine resulted in a 100 % survival rate, improved radiographic outcomes, and statistically significant enhancements in clinical evaluations, biomarker analysis, and renal function measurements [85].

Both NSAIDs and acetaminophen have been found to significantly impact the expression of both the SARS-CoV-2 entry gene and the arachidonic acid metabolizing gene mRNA expressions [18]. In a 14-day treatment with NSAIDs (ibuprofen and diclofenac) or acetaminophen on mouse lungs, it was observed that these medications did not induce any pathological changes in the mouse lung tissue. Furthermore, it was noted that acetaminophen led to the downregulation of human CTSL and TMPRSS2 gene expression. Inhibition of CTSL and TMPRSS2 has been demonstrated to prevent and reduce the severity of SARS-CoV-2 infection. CTSL protease is responsible for cleaving the S-glycoprotein at the attachment point between the SARS-CoV-2 virus and the ACE-2 receptor on the host cell [51]. TMPRSS2 plays a critical role in breaking down the spike protein on the virus's surface, which is essential for the virus to attach to and enter host cells. Once the spike protein is cleaved, the virus can fuse with the host cell's membrane and release its genetic material into the host cell [86,87].

Moreover, acetaminophen has been observed to significantly reduce the expression of SARS-CoV-2 genes, including the alox12 gene, responsible for producing leukotrienes that can cause bronchoconstriction. Additionally, acetaminophen was found to decrease

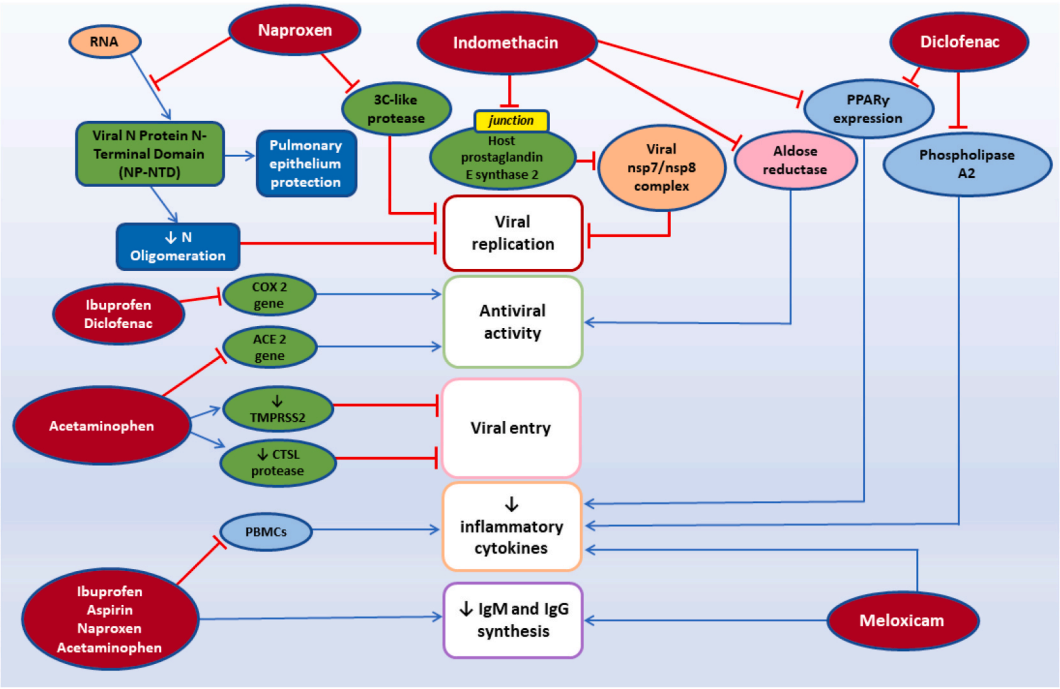


Fig. 3. The potential effects of NSAIDs, aspirin, and acetaminophen in terms of inhibition of viral replication and viral entry, antiviral activity, reduction in inflammatory cytokines, and antibody synthesis.

the expression of cyp2j5 and cyp4a12. The cyp2j5 gene is responsible for metabolizing arachidonic acid into epoxyeicosatrienoic acids (EETs), which can lead to pulmonary vasoconstriction and hypoxia. Cyp4a12 expression has been associated with patients suffering from hypoxia and vasoconstrictive conditions [18]. The mechanisms of action of these NSAIDs discussed above are visually illustrated in Fig. 3 and summarized in Table 1 with the chemical structures.

5.1. Dual immunomodulation by NSAIDs: the evidence of relevance and validity in SARS-CoV-2 usage

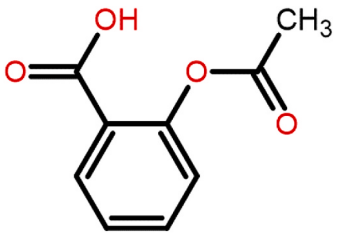
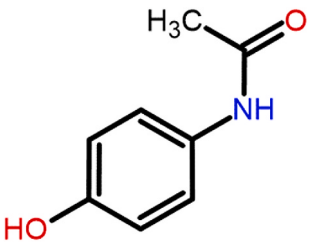
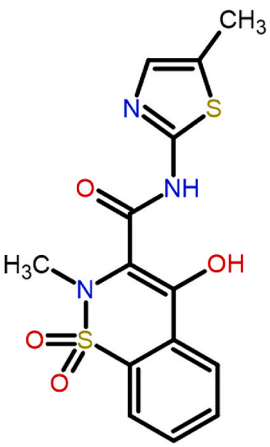
NSAIDs exhibit complex roles in viral and bacterial infections [88] including their effects in the context of SARS-CoV-2 infection. These drugs demonstrate dual immunomodulatory actions, stimulating interferon, nitric oxide, and T lymphocytes while inhibiting macrophages, neutrophils, and antibody formation [89,90]. Notably, NSAIDs possess the capacity to modulate the immune system through various mechanisms. Specifically, they can inhibit the synthesis of certain cytokines, pivotal in the immune response to infectious agents, leading to a diminished inflammatory response. This attenuation of inflammation may be beneficial in certain contexts but also has the potential to impede the body's innate capacity to combat viral infections [91].

In the realm of anti-tumor immunity [92], NSAIDs are known to modulate the immune response, particularly by inhibiting COX-2/PGE2 signaling [93]. This action is believed to enhance the effectiveness of immunotherapy treatments. Additionally, NSAIDs influence the p38 MAPK pathway, critical in the inflammatory response to SARS-CoV-2. Inhibitors of this pathway, including NSAIDs, impact proinflammatory cytokine production and may offer therapeutic benefits in managing severe cases of cytokine storm associated with COVID-19 [94].

Furthermore, NSAIDs are frequently employed in the management of fever and pain, symptoms commonly associated with viral infections like COVID-19, offering symptomatic relief. However, the practice of fever reduction through NSAIDs has sparked scientific debate. Concerns center on whether this intervention might disrupt the body's intrinsic defense mechanisms against infections, given that fever is part of the body's natural response to such challenges [91]. The World Health Organization's analysis suggests a minimal link between NSAIDs and acute viral respiratory infections. While uncertainties linger about stroke, heart attack risks, and certain adverse events, most studies reported minimal adverse effects. Moreover, NSAIDs do not affect the expression of ACE-2, a crucial receptor for SARS-CoV-2 entry into cells, nor impact viral entry or replication in vitro [95]. A retrospective cohort study involving 38 centers concluded that NSAID use does not significantly affect clinical outcomes in COVID-19 patients [19].

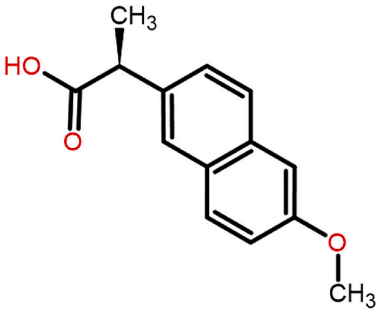
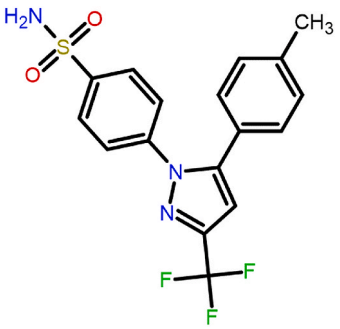
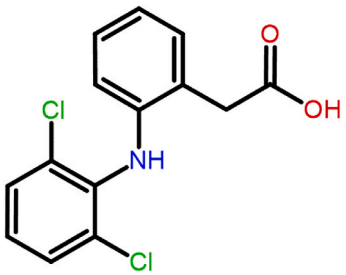
Additional investigations through randomized controlled trials are imperative to fortify these findings [95]. Detailed mechanistic studies probing the molecular interactions between NSAIDs and SARS-CoV-2 are pivotal for deeper comprehension. Exploration into the long-term ramifications of NSAID utilization among COVID-19 patients holds significance, as does research across diverse demographic cohorts and comparative analyses of different types of NSAIDs in the context of COVID-19 management [19,95]. Refer to Fig. 4 for visual representation.

Table 1
The main NSAIDs, aspirin, and paracetamol discussed in this review with their chemical structures and anti-viral mechanisms.

Chemical structure	Drug name	Major anti-viral mechanism
	Aspirin	• Reduces the synthesis of IgM and IgG antibodies in human peripheral blood mononuclear cells
	Acetaminophen (paracetamol)	• It binds weakly to the N-dimer of the virus without inducing any modification in N oligomerization or demonstrating antiviral effects. • It significantly reduces the expression of SARS-CoV-2 genes, including those responsible for bronchoconstriction and vasoconstriction, indicating its potential impact on viral replication and pathogenesis
	Meloxicam	• Reduces the synthesis of IgM and IgG antibodies. • Inhibits pro-inflammatory cytokines.

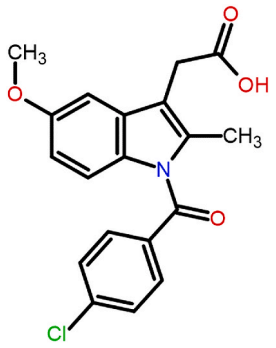
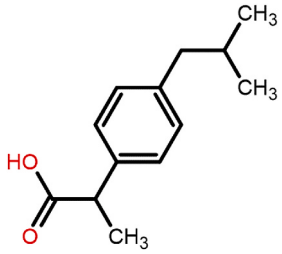
(*continued on next page*)

Table 1 (*continued*)

Chemical structure	Drug name	Major anti-viral mechanism
	Naproxen	• Naproxen interferes with viral replication by inhibiting the 3C-like protease, which is crucial for the viral synthesis of SARS-CoV-2 • Reduces the synthesis of IgM and IgG antibodies in human peripheral blood mononuclear cells • Targets the coronavirus N protein N-terminal domain (N NTD) and competes with RNA for the binding site • Inhibits the oligomerization of the N protein, targeting the monomeric NP at its RNA binding groove and consequently hindering the formation of the NP-RNA complex.
	Celecoxib	• This COX-2 inhibitor exhibited tighter binding to the monomeric N protein of the virus compared to naproxen, suggesting a potential role in inhibiting viral replication. • At low concentrations, celecoxib might enhance N oligomerization/aggregation, indicating a complex role in viral infections. • Affects the replication and dissemination of viruses, primarily through elevating nitric oxide concentration and subsequently suppressing COX enzyme activity. • Stabilizes the dimeric interface and exhibits a tight binding to the monomeric N protein.
	Diclofenac	• In vitro and in vivo studies have shown that diclofenac can suppress the activation of the NLRP3 inflammasome. • Displays antiviral activity by inhibiting the expression of PPAR-γ, which may mitigate the production of inflammatory cytokines.

(*continued on next page*)

Table 1 (*continued*)

Chemical structure	Drug name	Major anti-viral mechanism
	Indomethacin	• Exhibits inhibitory effects on prostaglandin E synthase 2 and IL-6 expression, suggesting its potential role in alleviating the cytokine storm associated with COVID-19. • Affects the replication and dissemination of viruses, primarily through elevating nitric oxide concentration and subsequently suppressing COX enzyme activity.
	Ibuprofen	• Although it does not significantly influence ACE-2 expression, viral entry, or replication, it may affect COVID-19 outcomes by attenuating the inflammatory response and modulating the production of protective antibodies. • Reduces the synthesis of IgM and IgG antibodies.

6. The nexus of viral infection, metabolic acidosis, and NSAID-induced effects

Viruses, inherently metabolically inert, rely on the metabolic processes of their host cells for replication. This dependency leads to various metabolic changes within the host, such as increased glucose metabolism (Warburg effect), alterations in lipid metabolism shifting from fatty acid oxidation to synthesis, and changes in tricarboxylic acid (TCA) cycle activity [96]. These alterations are crucial for the viral life cycle, and their mechanisms can be observed in several viral infections. For instance, HIV infection results in heightened aerobic glycolysis and glutaminolysis in T cells [97], while the Dengue virus exploits host cell lipid reserves to facilitate TCA cycle activity, aiding its replication [98]. Zika virus in neuronal cells triggers the induction of immune responsive gene 1 (IRG1), affecting succinate dehydrogenase and thus influencing cell survival [99]. Hepatitis C virus initially boosts glycolysis pathways and enhances glucose utilization, before switching to utilizing host cell amino acids [100]. Moreover, Human cytomegalovirus (HCMV) and herpes simplex virus (HSV) exhibit distinct impacts on host metabolism, further underscoring the varied nature of viral metabolic reprogramming [101].

In response to viral infections, host cells produce interferons, which instigate a range of metabolic changes that can counteract the metabolic reprogramming imposed by viruses [100]. The activation of interferon receptors leads to the expression of interferon-stimulated genes, which significantly impact cellular metabolism and consequently influence the outcome of a viral infection. These effects include alterations in cholesterol and lipid metabolism, which can inhibit the replication of certain viruses, such as HIV-1 [102]. This interplay between viral-induced metabolic changes and IFN-driven metabolic responses highlights potential avenues for targeting viral infections through metabolic pathways.

Moreover, the intersection of metabolic disorders and viral infections has become increasingly apparent. Individuals with diabetes mellitus (DM) and obesity are at heightened risk for severe outcomes from viral infections, including COVID-19. In these patients, there is an increased likelihood of hospitalization, the necessity for mechanical ventilation, and higher mortality rates [103,104]. Notably, the efficacy of influenza vaccinations is also diminished in obese individuals [105]. These observations emphasize the need for a deeper understanding of the metabolic status in the management of viral infections and vaccine effectiveness.

Consequently, targeting specific metabolic pathways emerges as a promising strategy for controlling viral infections. This approach can include the use of drugs that target particular metabolic pathways, dietary modifications to influence metabolism, and leveraging the metabolic needs of the immune system [96]. For example, drugs that impede lipid metabolism such as statins can be effective against viruses dependent on these pathways [106]. Dietary interventions, such as fasting or ketogenic diets, have shown the potential to modulate outcomes of viral infections [107]. Furthermore, a thorough understanding of the metabolic requirements of immune cells

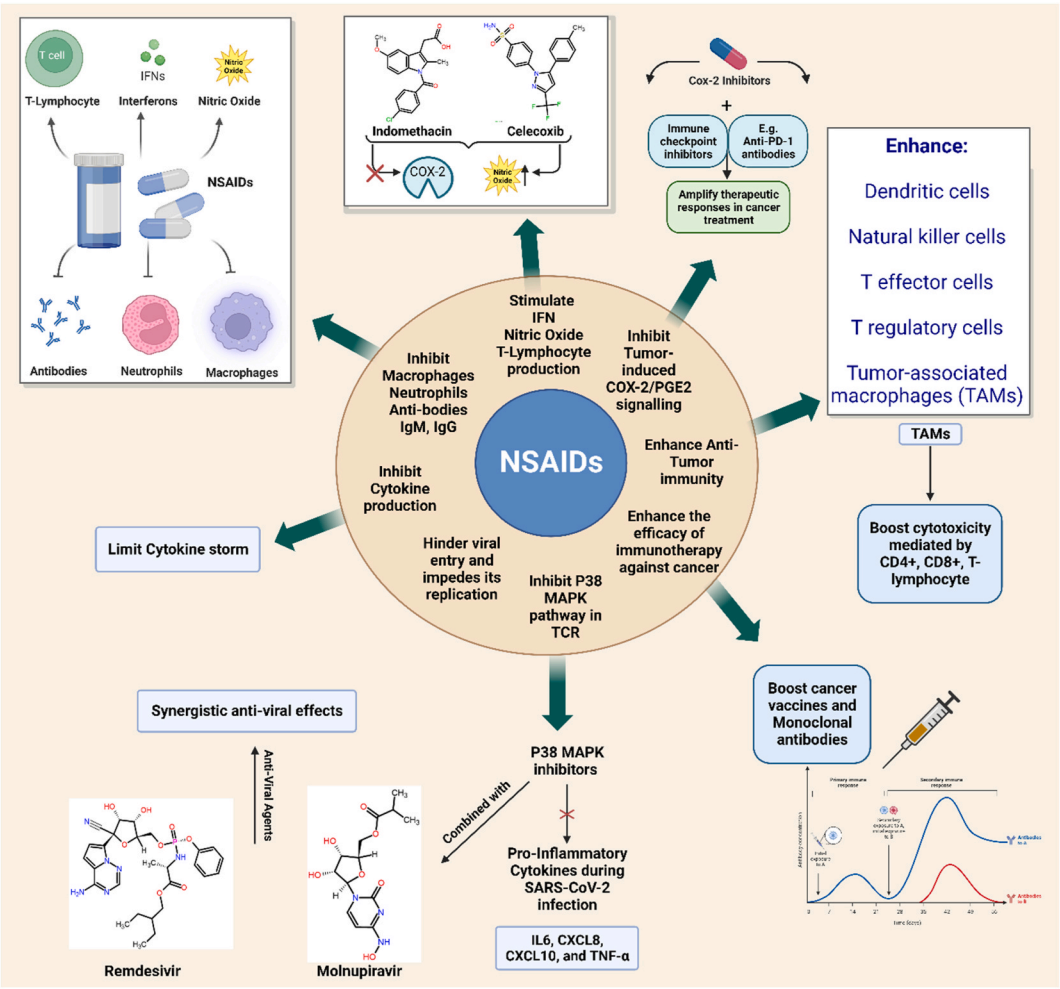


Fig. 4. Immunomodulatory effects of NSAIDs in tumor management and viral infections, providing an overview of the synergistic potentials when combined with various therapeutic agents.

can inform strategies to bolster their effectiveness against viral infections, exemplifying the integration of metabolism-focused approaches in antiviral strategies [108].

The complex interplay between viral infections and host cell metabolism, particularly the shift towards augmented glucose metabolism as explained in the examples above, underscores the potential of metabolic interventions in the management of viral diseases. This metabolic reprogramming, prominently observed in host cells infected with viruses like SARS-CoV-2, predisposes to an increased risk of metabolic acidosis [109]. This risk is further exacerbated in individuals with pre-existing metabolic disorders such as DM and obesity. The virus-induced metabolic shift towards glycolysis, coupled with the impaired metabolic flexibility in these patients, can lead to an accumulation of acidic metabolic byproducts, thereby heightening the likelihood of metabolic acidosis [110]. This observation necessitates a comprehensive approach to treatment and prevention strategies for viral infections, one that incorporates a nuanced understanding of metabolic alterations and their implications, particularly in the context of metabolic acidosis. This approach not only targets the viral pathology but also addresses the metabolic derangements that contribute to the disease's severity and progression.

Acquired distal renal tubular acidosis (RTA) is associated with the use of NSAIDs, characterized by impaired distal acidification of urine due to a reduction in net hydrogen ion secretion in the distal nephron. The primary mechanism by which NSAIDs like ibuprofen induce metabolic acidosis is linked to their impact on renal function, specifically affecting renal tubular processes [111]. It has been observed that ibuprofen, a commonly utilized NSAID, is associated with the development of hypokalemia and metabolic acidosis. These conditions arise due to the drug's influence on renal function. Notably, the occurrence of hypokalemia and acidosis is not limited to the consumption of very high doses of ibuprofen; it can also occur with moderately high or even normal doses. These complications are typically of renal origin, and the discontinuation of ibuprofen usually results in the resolution of hypokalemia and acidosis within days. However, in some instances, the impact of ibuprofen on renal function can be severe and potentially fatal [112].

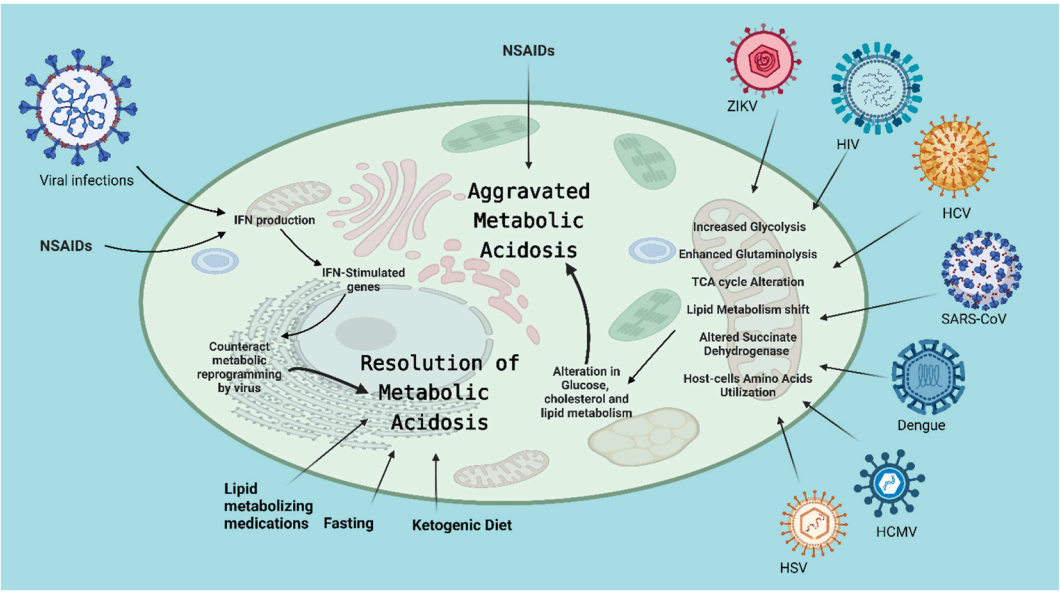


Fig. 5. Overview of viral exploitation of host metabolic processes and the host's immunometabolic response. This figure displays how viruses manipulate host cell metabolism, including increased glucose and altered lipid metabolism. The host's interferon response and the metabolic consequences, including the effects of NSAIDs on metabolic acidosis, are also illustrated.

While both COX-1 and COX-2 inhibitors can potentially lead to metabolic acidosis through renal impairment, the risk may differ based on the specific drug, dosage, duration of use, and patient's renal function. COX-1 inhibitors might present a higher risk due to their broader impact on renal prostaglandins, which are crucial for maintaining normal renal function and blood flow [113,114]. On the other hand, evidence was not found for a clinical association of increased COVID-19 severity with diclofenac, meloxicam, and celecoxib, selective for COX-2, suggesting the possibility of agent-specific risk profiles for individual COX inhibitors [19]. COX-2 inhibitors, while generally considered safer in terms of gastrointestinal side effects, can still affect renal function and acid-base balance, especially in susceptible individuals. Recent studies have highlighted the kidney as the principal site where local COX-2 regulates blood flow, identifying a previously unreported PPARβ/δ-mediated renal vasodilator pathway as the involved mechanism [115].

Theoretically, NSAIDs, through their action on COX enzymes, could affect the production of interferons, thereby influencing the body's ability to counteract viral-induced metabolic changes. However, this area of research is notably underexplored, with a significant gap in our understanding of how NSAIDs may directly or indirectly stimulate interferon production and their subsequent effect on the metabolic alterations caused by viral infections. This gap underscores the need for focused scientific investigations to elucidate the potential interplay between NSAIDs, interferon response, and metabolic regulation in the context of viral infections. Such research could offer new insights into the therapeutic strategies for managing viral infections and their associated metabolic complications. Refer to Fig. 5 for the interplay of viral metabolic exploitation and host response.

7. Conclusion and perspectives

The use of NSAIDs in the context of viral and bacterial infections has been a subject of debate and investigation. This review provides an overview of the effects of NSAIDs on various aspects of infection, including viral replication, immune responses, and inflammatory processes. Studies have indicated that NSAIDs can modulate immune responses by reducing the recruitment of inflammatory cells and cytokine release during inflammation. Additionally, they can compromise the antiviral defense activity of innate immune cells and subsequently inhibit the production of certain cytokines. Notably, specific NSAIDs have demonstrated the ability to inhibit the replication and spread of certain viruses by increasing nitric oxide concentration and limiting COX enzyme activity. Furthermore, this article discusses the mechanisms of COX-2 activation in the coronavirus family and potential therapeutic targets and the involvement of SARS-CoV-2 infection in various pathways, including ERK/NF-κB and PI3K/PKCε/JNK/CREB, which contribute to enhancing the inflammation state.

The role of ACE-2, the imbalance in the RAAS, and the binding of the virus to ACE-2 receptors were discussed concerning SARS-CoV-2 infection, cytokine storm, and elevated production of inflammatory mediators. This imbalance can be influenced by factors such as age, sex, and comorbidities. The immunomodulatory effects of NSAIDs in SARS-CoV-2 infection are addressed as well. NSAIDs can affect the production of proinflammatory cytokines and may have potential benefits in reducing the cytokine storm. Specifically, the modulation of the RIG-1 gene and NLRP3 inflammasome, both involved in immune responses to viral infections and inflammation, presents a promising approach to potentially suppress COX-2 expression and its associated inflammatory processes, thereby serving as viable targets for viral infections.

Understanding the effects of NSAIDs on viral and bacterial infections is crucial for optimizing therapeutic strategies and managing potential complications. Further research is needed to elucidate the specific mechanisms underlying these effects and evaluate the clinical implications of NSAID use in infection scenarios. For instance, exploring the potential interactions and synergistic effects of NSAIDs with other antiviral or antibacterial agents is one of the main areas that can enhance therapeutic outcomes against emerging viral infections. By further examining the underlying mechanisms of COX-2 activation in different coronaviruses including SARS-Cov-2 specific therapeutic targets can be identified and targeted to achieve a satisfactory response with fewer adverse effects. RIG-1 gene and NLRP3 inflammasome are showcased in this review as potential targets in SARS-CoV-2 infections, however, unraveling other targets could be a key factor in attenuating excessive inflammation without compromising the host's antiviral defense mechanisms.

This review highlights the complex interplay between viral infections and host metabolism, particularly the shifts in glucose, lipid, and amino acid metabolism during viral infections like SARS-CoV-2. It underscores the potential of metabolic interventions in managing these infections and details the risk of metabolic acidosis, especially in patients with pre-existing metabolic disorders. Furthermore, the review addresses the impact of NSAIDs on renal function and metabolic acidosis, emphasizing the need for focused research on NSAIDs, interferon response, and metabolic regulation in viral infections. We aim of this article is to provide updated insights into the interactions between NSAIDs and SARS-CoV-2 infections, aiming to mitigate the risk of future pandemics as highlighted by recent warnings from the World Health Organization.

Ethics approval and consent to participate

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Consent for publication

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Availability of data and materials

Not applicable.

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CRediT authorship contribution statement

Said Moshawih: Writing – original draft, Visualization, Formal analysis, Data curation, Conceptualization. **Qais Jarrar:** Conceptualization. **Abdul Alim Bahrin:** Writing – original draft, Data curation. **Ai Fern Lim:** Writing – review & editing, Visualization, Data curation. **Long Ming:** Writing – review & editing, Supervision. **Hui Poh Goh:** Writing – review & editing, Supervision, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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