

# NSAIDs: A Double Edged Sword in Viral Infections

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## Abstract

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) are used as analgesics and antipyretics in viral infections, as supportive therapy is the mainstay of treatment. However, their role in the course of the illness is still ambiguous. Several experimental evidences carried out on various viral infections about the role of NSAIDs in the course of illness are contradictory; some reported possible antiviral effects and some negate it. NSAIDs inhibit PGs and also have their own actions on immune system and viruses. NSAIDs have stimulatory effects on T lymphocytes, Nitric Oxide (NO) and interferons, but inhibitory effects on neutrophils, macrophages and antibodies formation. NSAIDs are used as adjunctive treatment in infectious diseases in which cytokines storm plays a role in the pathogenicity. However, in other studies their effects on immune system were associated with unresolved symptoms and complications. The worth saying in this entity is the evidence-based studies of antimicrobial activity of NSAIDs. NSAIDs are proven to inhibit the entry of virus to the cells like in ZIKV, as well as they inhibit the replication of many viruses like the inhibitory effect of naproxen on SARS-CoV-2 replication. However, they fail to show any direct antiviral activity in adenovirus infections, and Ibuprofen increases the shedding of RSV in a bovine model. Indeed, there are many contradictory published studies between various viruses, patients' cases, and whether it's a study on animals or humans. More randomized clinical trials are mandatory to exactly elucidate if use of NSAIDs, during viral infections especially COVID-19, modify and abort the course of viral infection by exerting beneficial therapeutic effects or the use of them is accompanied by delirious hazards and negatively impact the health of the patient.

**Keywords:** Antiviral Activity, Controversial, COVID-19, Immunomodulatory, NSAIDs, Viral Infection

## Introduction

Viruses vary in virulence, ranging from viruses that cause subclinical or clinically unapparent infections to those that cause disease to those that cause death.<sup>1</sup> Many viral infections distress humans and are associated with increase in morbidity and mortality. For example, herpes viruses may cause painful skin ulcers, chickenpox, Kaposi's sarcoma or encephalitis<sup>2</sup>. In acute exacerbation of Chronic Obstructive Pulmonary Diseases (COPD), viral infections play an important role in the course of the disease.<sup>3</sup> Viral infection is one of etiologies to sudden sensorineural hearing loss.<sup>4</sup> Also, Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2), which originated in the end of 2019, has led to an outbreak that globally extended causing higher risk of mortality in patients with chronic diseases.<sup>5</sup>

Antiviral drugs are used for the treatment of a limited number of infections. Therefore, the backbone treatment of viral infections is supportive therapy. In addition, NSAIDs may be used to relieve accompanying symptoms

of pyrexia and pain.<sup>6</sup> But recently, the debate is raised about the risk of using NSAIDs in viral infections, and whether they have protective or worsening effects in the treatment.<sup>7</sup>

NSAIDs are used whenever pain, fever, and undesired inflammation is present<sup>8</sup>. Paracetamol and NSAIDs are used in osteoarthritis as analgesic and as anti-inflammatory drugs.<sup>9</sup> NSAIDs are used as antipyretic agents because sometimes the physical cooling methods aren't enough.<sup>10</sup> In terms of analgesic effect, a study suggested that paracetamol should be considered as the first line analgesic for both acute and persistent pain, and if not sufficient, then other NSAIDs should be used concomitantly with caution.<sup>11</sup> In spite of their many therapeutic benefits; NSAIDs like any drugs, have their well-known side effects and complications including their deleterious gastrointestinal and cardiovascular effects.<sup>12</sup>

Since the COVID-19 pandemic, the urge is broadly

raised about the effect of using ibuprofen in viral infections; even there was no scientific evidence that ibuprofen or other NSAIDs worsen the infection<sup>13</sup>. However, based on data the studies on this matter are very contradictory. Some studies reveal beneficial antimicrobial effects of NSAIDs in infections generally and others reveal worsening effects. Regarding the positive viewpoints, naproxen has inhibitory effects against influenza A and SARS- COV-2, by preventing the viral replication and protecting the bronchial epithelium.<sup>14</sup> A possibility for COX2 enzyme to be included in pathogenesis of H5N1 infection has demonstrated, and thus COX2 inhibitors may be used as adjunctive treatments along with antiviral drugs.<sup>15</sup> NSAIDs have immunostimulant effects by inhibiting the PGs that suppress T lymphocytes.<sup>16</sup> NSAIDs increase NO production and inducible Nitric Oxide Synthase (iNOS) expression,<sup>17</sup> and the significance is that NO has an antiviral activity.<sup>18</sup> A previous study showed that acetaminophen and ibuprofen have antibacterial activity.<sup>19</sup>

On the other hand, some studies have negative viewpoints. For example, NSAIDs shows an inhibitory effect on human neutrophils activity<sup>20</sup> and to a less degree on macrophages.<sup>16</sup> NSAIDs lower the body synthesis of antibodies if administered after infections or vaccinations.<sup>21</sup> Ibuprofen increases viral shedding.<sup>22</sup> Ibuprofen was associated with increase in the reconsultations because of symptoms progression and complications.<sup>23</sup> Masking effects of NSAIDs may delay the diagnosis of some infectious diseases which may affect the prognosis negatively.<sup>24</sup> NSAIDs could exacerbate the patients' status of group A streptococcal infection into toxic shock and multi-organs dysfunction because of its effect on the immune system and decreasing cardinal manifestations.<sup>25</sup>

So, it's apparent that using NSAIDs in viral infections is a controversial matter, and thus the present mini-review aims at providing an overview about the role of NSAIDs in viral infections specifically, by summarizing the current stage of knowledge of their use risks and benefits that are reported in literature.

NSAIDs are a FDA-approved drug class for relieving pain, inflammation and fever.<sup>26</sup> They showed high potency as anti-inflammatory and analgesic drugs, for which they are the most widely used medications in the world.<sup>27</sup> Their effectiveness has been proved in many diseases, including acute attack of migraine<sup>28</sup> osteoarthritis,

rheumatoid arthritis,<sup>29</sup> dysmenorrhea,<sup>30</sup> low back pain<sup>31</sup> and ankle sprain.<sup>32</sup> Depending on this wide range of use and through their mechanism on blockade of the enzyme Cyclooxygenase (COX), which is an enzyme that is work to form prostanoids, including thromboxane and prostaglandins , from arachidonic acid.

Beside their known anti-inflammatory role, Fukunaga et al., by their experimental murine model of acute lung injury, demonstrated that COX-2 inhibition was associated with a reduction in the recruitment of Polymorphonuclear (PMNs) leucocytes in the lungs, with a prolonged lung infiltration and delayed recovery.<sup>33</sup> Similarly, in a rat model of carrageenin-induced pleurisy, either selective COX-2 or nonselective COX-1/COX-2 inhibition reduced inflammatory cell numbers and exudate formation within the pleura at 2 h, but exacerbated pleural inflammation at 48 h.<sup>34</sup> From the point of anti-inflammatory action of NSAIDs, Ibuprofen suggested to be safe and effective in the case of SARS-CoV-2 infection in selected patients with low risk of NSAID-related complications through its multiple anti-inflammatory effects, but not limited, to the down regulation of inflammatory pathways such as NF- $\kappa$ B and inhibition of pro-inflammatory cytokines interleukin-6 (IL-6) and Tumor Necrosis Factor- alpha (TNF $\alpha$ ).<sup>35</sup>

A wide variety of studies on antiviral activity of anti-inflammatory drugs was evolved. Many preclinical studies carried out both *in vitro* or on animals suggested the role of NSAIDs in fighting viral conditions. Previous studies observed that COX-2 and COX-1 deletion leads to reduction of mortality in mice infected with influenza A and with worsening of infection, respectively.<sup>36</sup> However, it is still controversial as there are many studies indicating the non-protective role of COX/NSAIDs during infections.<sup>33,34,37,38</sup> However, the evidence of their efficacy on combination with other antiviral drugs is still more significant than its limitation.<sup>39</sup> This is why it is still worth studying the antiviral effect of the non-steroidal drugs especially after evolving many dangerous and non-curable viral diseases that generally replicate and spread through blocking the host antiviral response.<sup>40</sup>

### **Controversy about the Potential Antiviral Activity of NSAIDs**

Potential antiviral activity of NSAIDs remains controversial. For instance, in a study were the antiviral properties of naproxen evaluated against SARS-CoV-2

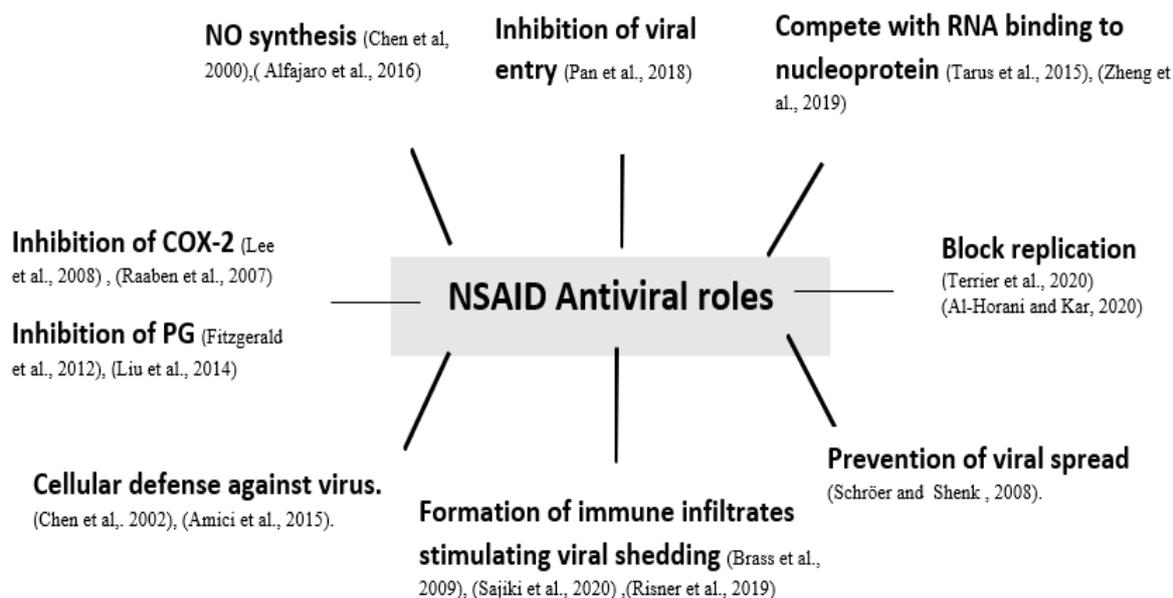
**Table 1.** Important Conclusions of the Recent Studies about Use of NSAIDs during COVID-19 Infection

Study	Finding	Explanation
Abu Esba et al., 2020	NSAIDs, as ibuprofen, are not proved to worsen the SARS-CoV-2 infection.	There is no significant correlation between mortality related to COVID-19 and both acute and chronic exposure to NSAIDs in regard to clinical improvement or length of stay in hospitals.
Terrier et al., 2020	Naproxen has antiviral properties against SARS-CoV-2.	Naproxen was found to inhibit viral replication in VeroE6 cells and human lung epithelium in a molecular modeling of SARS-CoV-2 infection and by its effect on the nucleoprotein-mediated replication, it protected the bronchial epithelium against SARS-CoV-2 induced-damage too.
Smart et al., 2020	Ibuprofen can be safely and effectively used in SARS-CoV-2 infection in selected patients with low risk of NSAID-related complications.	Via playing multiple anti-inflammatory roles as down regulation of inflammatory pathways and inhibition of pro-inflammatory cytokines, ibuprofen suggested to be used in SARS-CoV-2 infection.
Al-Horani and Kar, 2020	The literature found that NSAIDs is a potential anti-viral medication that has therapeutic effect against SARS-CoV-2.	It was explained in the study by being NSAIDs have immune-modulatory effects in the severe cases of COVID-19 by interfering with the post-entry events of the viral cycle.
Weikle, 2020	The study reported that there is no scientific evidence about worsening the COVID-19 infection by the use of Ibuprofen.	Based on consulting with physicians dealing with COVID-19 patient and studies that none of them report negative effects of Ibuprofen, WHO does not recommend against the use of ibuprofen.

in a molecular modeling, it is founded that naproxen inhibited viral replication in VeroE6 cells and human lung epithelium models of SARS-CoV-2 infection and protected the bronchial epithelium against SARS-CoV-2 induced-damage by its effect on the nucleoprotein-mediated replication.<sup>14</sup> This finding has been emphasized by a comprehensive review which concludes NSAIDs as potential anti-viral therapeutics against SARS-CoV-2 by interfering with the post-entry events of the viral cycle<sup>41</sup>. Tarus et al. concludes that naproxen has an anti-viral effect in addition to its anti-inflammatory effect against influenza A virus by competing with the RNA binding to the virus.<sup>42</sup> Moreover, *in vivo* and *in vitro* study showed that naproxen is a potential broad anti-influenza virus drug, as it inhibits influenza B virus replication through multiple mechanisms by targeting.<sup>43</sup> A study by Pan et al. has revealed that several NSAIDs; including aspirin, ibuprofen, naproxen, acetaminophen, and lornoxicam, significantly inhibited the entry of Zika Virus (ZIKV) and consequently its replication. This was exerted by reducing the expression of the entry cofactor of ZIKV.<sup>44</sup> NSAID's antiviral activity was also observed in many other viruses, for example they were effective in antagonizing propagation of Vesicular Stomatitis Virus (VSV), responsible for encephalitis, both *in vitro* and *in vivo*. *In vitro* experiments

showed that VSV-infected mice treated with celecoxib expressed more Nitric Oxide Synthase (NOS)-1 and consequently produced more NO compared to the control animals. NO is known to inhibit replication of VSV.<sup>45</sup> The same mechanism was also reported by a group of researchers, regarding sapovirus, in which the inhibition of COX-2 considerably increased the production of NO, causing a reduction in porcine sapovirus (pathogen responsible of severe acute gastroenteritis) replication, suggesting possible new targets for the treatment of sapovirus infection.<sup>46</sup> The protective effects of NSAIDs were also documented by a study of Fitzgerald et al. who reported that the Human Immunodeficiency Virus (HIV-1) infection is associated with increased cervical COX-2 and elevated systemic PGE<sub>2</sub> levels. Drugs that inhibit the synthesis of PGE<sub>2</sub> may prove useful in reducing the risk of cervical cancer or systemic inflammation in HIV-infected women.<sup>47</sup>

Moreover, further studies were carried out to understand the role of NSAIDs in Japanese Encephalitis Virus (JEV) propagation *in vitro*. When cells were treated with the Mitogen Activated Protein Kinase (MAPK) inhibitors, salicylate lost their antiviral effect. The activation of MAPK by anisomycin mimicked the action of salicylate in suppressing JEV-induced cytotoxicity.



**Figure 1.** NSAIDs Role as Antiviral Agents based on Clinical Researches. NSAID: Non-steroidal anti-inflammatory drugs, PG: Prostaglandins, COX-2: Cyclooxygenase-2, NO: Nitric Oxide, RNA: Ribonucleic acid.

The decreased phosphorylation of Extracellular Signal-Regulated Kinase (ERK) was induced by JEV infection and the decrease in ERK was reversed by salicylate. These data suggest that the signalling pathways of MAPK play a role in the antiviral action of salicylate.<sup>48</sup> Additional studies on the Venezuelan Equine Encephalitis Virus (VEEV), demonstrated the effectivity of celecoxib, tofacitinib, and rolipram in decreasing viral titers both after pre-treatment and post-treatment of infected cells. Celecoxib was also shown to decrease inflammatory gene expression.<sup>49</sup>

Furthermore, prostaglandins have been suggested to play an important role in the reactivation of latent herpes simplex virus. NSAIDs have been reported to suppress reactivation of herpes simplex virus-1 (HSV-1) in trigeminal ganglions. However, whether this drug can affect reactivation of HSV-1 in vestibular ganglions is unclear. A study was conducted that showed a decreased reactivation rate of HSV-1 by about 20%. Though, more *in vitro* or *in vivo* studies are needed to confirm the effects of the drugs.<sup>50</sup> Reassuring results were also obtained in a further study that used mice latently infected with HSV-1 with a conclusion that bromfenac eye drops can suppress HSV-1 reactivation.<sup>51</sup> Similarly, NSAIDs such as pranoprofen and bromfenac sodium, were documented to cause significant inhibition of HSV-1 reactivation and reduce inflammatory reaction *in vitro* and *in vivo*, and relief of corneal

inflammation and subsequent viral keratitis that has now become the most severe cause of blindness corneal disease worldwide.<sup>52</sup>

On top of all of that, NSAIDS such as tolfenamic acid and indomethacin have been demonstrated to markedly reduce direct cell-to-cell spread of human Cytomegalovirus (CMV) in cultured fibroblasts (which is the basis of pathogenesis). The block is reversed by adding prostaglandin E2. NSAIDS are suggested to control human CMV infections in conjunction with other anti-viral treatments.<sup>53</sup> Sajiki et al. also evaluated the effect of COX inhibitors in Bovine Leukemia Virus (BLV); a chronic viral infection of cattle and endemic in many countries, including Japan, and concluded that inhibition of PGE<sub>2</sub> production using a COX-2 inhibitor, activated BLV-specific Th1 responses *in vitro*, as evidenced by enhanced T cell proliferation and Th1 cytokine production, and reduced BLV proviral load *in vivo*. Combined treatment with the COX-2 inhibitor meloxicam and anti-programmed death-ligand 1 Ab significantly reduced the BLV proviral load, suggesting a potential as a novel control method against BLV infection.<sup>54</sup>

COX2 is highly induced in epithelial cells of lung tissues obtained from autopsy of patients who died of avian influenza H5N1 infection, revealing a possibility for COX2 enzyme to be included in pathogenesis of H5N1 infection, and for COX2 inhibitors to be adjunctive

treatment along with antivirals.<sup>15</sup> Data suggested the role of the non-selective COX inhibitor indomethacin in activating the double-stranded RNA (dsRNA)-dependent protein kinase R (PKR) in human colon cancer cells. Actually, PKR has an important role in the cellular defence response against viral infection which raised the possibility of its effectivity during infection with the prototype rhabdovirus vesicular stomatitis virus. By activating PKR, indomethacin causes shutting off viral protein translation and blocking viral replication and protects host cells from virus induced damage.<sup>55</sup>

Previous studies also investigated the role of COXs in Mouse Hepatitis Coronavirus (MHV) infection cycle. It was found that blocking COX activity by different inhibitors or by RNA interference reduced MHV infection thus, providing a potential target for anti-coronaviral therapy.<sup>56</sup> On the other hand, another study showed that the use of NSAIDs in patients with chronic viral hepatitis has only a “historical” interest. Nevertheless, the possible usefulness of ketoprofen with (pegylated-interferon) PEG-IFN and ribavirin for HCV infected patients, non-responders to standard therapy or with genotype 1, should be evaluated in future clinical studies.<sup>57</sup>

A previous study; from Massachusetts Institute of Technology and Harvard Medical School, showed that parecoxib, may increase the expression of interferon-inducible transmembrane protein IFITM3, Interferon-stimulated gene-15, Mx2, and antimicrobial peptides. Thereby, it may: (1) inhibit the replication of Hepatitis-B/C, Dengue, Zika, Ebola, HIV-1, Mtb, Malaria, CMV, Influenza H1N1, respiratory syncytial, Sindbis, and SFV viruses; (2) confer resistance against these infections and (3) promote innate immunity. Thus, pharmacological formulations encompassing “Parecoxib or its analogues, either alone or in combination with other drugs,” may be used to prevent/treat infections caused by Hepatitis-B/C, Dengue, Zika, Ebola, HIV-1, Mtb, Malaria, CMV, Influenza H1N1, respiratory syncytial, Sindbis, and SFV viruses.<sup>58</sup>

On the contrary to all the beneficial effects of NSAID's just mentioned, most recently, a study by Weikle reported no evidence that Ibuprofen worsens COVID-19 infection.<sup>59</sup> Previously, the results of a study of acute viral myocarditis on mice suggests that ibuprofen worsens myocardial inflammation and necrosis during acute viral myocarditis.<sup>60</sup> These risks are supported

by other studies that showed how the use of NSAIDs is associated with an elevated risk of severe skin and soft tissue complications (mostly cellulitis and abscess) of varicella zoster virus infection, mostly in children with varicella.<sup>61</sup> This was additionally supported by epidemiological studies that demonstrated an increased risk of skin infection focusing particularly on necrotizing fasciitis associated with the use of NSAIDs.<sup>62-64</sup> Another experimental study on New Zealand rabbit eyes treated topically with either ketorolac, diclofenac, prednisolone acetate demonstrated no direct adenoviral inhibitory activity, no prolongation of viral shedding, and no effect on the formation of immune infiltrates. These results suggest that anti-inflammatory drugs have no clinically significant direct antiviral activity against common adenoviral serotypes.<sup>65</sup> NSAIDs may increase the risk of empyema without antibiotics use.<sup>66</sup> The Internet Doctor trial for the self-management of respiratory infections found that increased Ibuprofen use is associated with symptoms progression.<sup>67</sup> Using NSAIDs may mask undiagnosed intensive care unit pneumococcal pneumonia symptoms and delay antimicrobial therapy and which in turn affect the outcome negatively.<sup>24</sup> NSAIDs could exacerbate the patients' status of group A streptococcal infection into shock and organ failure by inhibiting neutrophils functioning, increasing cytokines production, and attenuating the cardinal manifestations.<sup>25</sup>

### **Immunomodulatory Activities of NSAIDs**

Immunomodulatory effects at clinically available doses through affecting the production of Tumor Necrosis Factor (TNF)-alpha and NO by macrophage- and T cell mediated immune responses, intercellular adhesion, phagocytic uptake and lymphocytic proliferation.<sup>68</sup> Ramos et al. have demonstrated potential therapeutic benefit of anti-inflammatory drugs to limit the innate immune response in combination with their antiviral property to fix the tissue damage caused by the influenza viral infection.<sup>69</sup> It is worth mentioning that NSAIDs proved to have immune-modulatory effects in the severe cases of COVID-19.<sup>41</sup> SARS-CoV-2 infection triggers a local immune response, recruiting macrophages and monocytes that respond to the infection and release immune mediators and in some patients, the downstream of mediators is over-produced in COVID-19 patients leading to severe disease.<sup>35</sup> A recent study reported a deleterious role of cytokines storm in the high pathogenicity

of SARS-CoV and MERS-CoV.<sup>70</sup> Through inhibition of cytokine production, NSAIDs may have a role in the amelioration of dangerous impacts of cytokine overload during these viral infections. In a randomized placebo controlled trial of Ibuprofen for respiratory syncytial virus infection in a bovine model, Ibuprofen decreases COX, 12/15-LOX, and cytochrome P450 epoxygenase products in lung lymph nodes and modulates immune response by narrowing the range of Il-13, Il-17 and IFN- $\gamma$  gene expression in mediastinal lymph nodes. In addition, Ibuprofen increases viral shedding.<sup>22</sup> NSAIDs affect neutrophils immune activity in varying degrees according to NSAID used and a stimulus exposed. Specifically; when they were exposed to a chemoattractant, N-formyl-methionyl-leucyl-phenylalanine (FMLP), aspirin and piroxicam inhibited neutrophil aggregation, degranulation and O<sub>2</sub><sup>-</sup> generation, whereas ibuprofen inhibited only aggregation and degranulation and indomethacin inhibited aggregation. When they are exposed to a tumour promotor, Phorbol Myristate Acetate (PMA) or a lectin, concanavalin A (Con A) none of the agents inhibited aggregation or degranulation induced by PMA or Con A: only piroxicam inhibited O<sub>2</sub><sup>-</sup> generation in response to them.<sup>20</sup> NSAIDs lower the body synthesis of antibodies if administered a few days after infections or vaccinations.<sup>21</sup> NSAIDs inhibit the expression of IL-4 in CD4 T cells and this can influence the adaptive immune response<sup>37</sup> and weakens the early production of IFN- $\gamma$  by innate immune cells that represents an effective mechanism for defence against viruses.<sup>38</sup>

### NSAIDs and Respiratory Viral Infections

Acute respiratory tract infections account for most of the mortality and comorbidity.<sup>71</sup> Monto emphasized in his paper that regardless to age and gender, the acute respiratory tract infection are the most common illnesses depending on studies and surveys conducted from the beginning of the 20<sup>th</sup> century.<sup>72</sup> Although, acute respiratory tract infections can be caused by a variety of etiologies, but viral infections are strongly associated with it especially the most important are the ortho- and paramyxoviridae, picornaviridae, coronaviruses, and adenoviruses.<sup>73</sup> In addition, through a study conducted on eighty adults with acute lower respiratory tract infection, the majority are found to be viral illness.<sup>74</sup> Viral respiratory tract infection can be in the upper or lower respiratory tract. Nasopharyngitis, pharyngitis,

tonsillitis and otitis constitute the upper respiratory tract infections which has been estimated by Neemisha Jain et al. in a study to be 87.5% of the total episodes of respiratory infections.<sup>75</sup>

By viral infection of respiratory tract, the virus enters the cell by group of cellular interaction with respiratory cell receptors, more specifically ICAM integrin, N-acetyl neuraminic acid, glycosaminoglycans and glycolipids, and molecules of the major histocompatibility complex, and some viruses such as SARS-CoV-2 interact with ACE-2 (Angiotensin Converting Enzyme -2) as a potential entry receptor which Zhou et al. showed in his study on ACE-2 receptors of humans, Chinese horseshoe bats, civet cats, and pigs cells. This interaction is mediated by many surface proteins which could be a target of treatment in some diseases as examples envelope glycoproteins and in naked viruses, the capsid proteins. Cell damage then take place either directly by viral replication and innate or adaptive immune response of the host through inflammatory mediators or by Cytopathic Effect (CPE) that occur in both the cells of living organisms and *in vitro* culture cells. The damaging of the cells of respiratory tract can happen in many ways such as membrane damage by the entry of viral particles, cytoskeleton changes that occur with viral and cellular proteins that synthesized during infection. Some viruses allow the fusion between neighbouring cells by having structural proteins (e.g. F protein) as in case of Respiratory Syncytial Virus (RSV), while other viruses cause changes at nuclear level that lead to the disintegration of the chromatin of infected cells.<sup>76,77</sup>

Some viral infection induce cytokine storm, in which release of inflammatory cytokines from leukocytes will induce more new cytokine production that will in turn cause cell and organ damage, in an attempt to destroy the invader and restore homeostasis of the body<sup>78</sup>. Ye et al. concluded that SARS-CoV-2 induces excessive and prolonged cytokine responses in critically ill infected individuals with COVID-19 which in turn causes acute respiratory distress syndrome or multiple-organ dysfunction which lead to physiological deterioration and death and most of these critically ill patients did not develop severe clinical manifestations in the early stages of the disease. However, the conditions of these patients deteriorated suddenly in the later stages of the disease or in the process of recovery<sup>79</sup>

*In vitro* cell experiments done in some studies on human macrophages and dendritic cells showed no increase in viral RNA in the cells, confirming that virus replication was abortive and no induction of apoptosis was detected in SARS-CoV-infected cells. However, they showed delayed release of cytokines and chemokines that occurs in respiratory epithelial cells, Dendritic Cells (DCs), and macrophages at the early stage of SARS-CoV infection. Later, the infected cells induced the expression of chemokines such as CXCL10/IFN-gamma-inducible protein 10 and CCL2/monocyte chemoattractant protein in macrophages and secrete low levels of the antiviral factors interferons (IFNs) and high levels of proinflammatory cytokines [interleukin (IL)-1 $\beta$ , IL-6, and tumor necrosis factor (TNF)] from dendritic cells.<sup>80,81</sup>

Although investigators and experts in the field recommend a variety of therapies for cytokine storm, there is no clinical studies that demonstrate the efficacy of a single agent in cytokine release syndrome in COVID-19 patients currently.<sup>82</sup> However, a literature in China concludes that treatment with corticosteroid, specifically methylprednisolone, may be beneficial for COVID-19 patients who develop ARDS.<sup>83</sup> A literature on 1984 demonstrate that *in vivo* administration of therapeutic dose of NSAID cause variable interference with the locomotion of elicited PMN depending on the type of inflammatory reaction and the used drug.<sup>84</sup> Previous studies found that when NSAIDs were given *in vivo*, it suppresses chemotaxis. However, they found that NSAIDs don't affect the chemotactic response of mature cells *in vitro*.<sup>85</sup> However, neither clinical data nor guidelines recommend the use of NSAIDs in respiratory viral infection as pneumonia or common cold even though they are commonly used to alleviate symptoms during them.<sup>86,87</sup> Also, a cohort study concludes that with delayed therapy of NSAIDs, the course of community acquired pneumonia will worsen that may associate with pleuropulmonary complications.<sup>88</sup> On the other hand, there is no conclusive evidence showing any additional risks for severe acute adverse outcomes associated with NSAIDs use in patients with viral respiratory infections, but this does not mean absence of such risks.

## Conclusion

Since the prevalence of COVID-19 pandemic, the urge is broadly raised about the clinical use of NSAIDs

in viral infections; whether it is safe to use them and if there any potential antiviral efficacy regardless of their antipyretic and analgesic known effects. The reports of many studies are really vague and contradictory. Some have proven its efficacy as antiviral agents for other viruses rather than COVID-19; in that they may interfere with viral entry, replication and RNA synthesis. Others were in line with their supportive role in that they alleviate symptoms especially those accompanying cytokines storm by their immune-modulatory activities. On the other hand, some studies observed worsening and deleterious impacts on the patient. Human randomized clinical trials are a mandate to decide potential antiviral efficacy of NSAIDs especially on COVID-19 patients with emphasis on pharmacogenetic studies to investigate their possible effect on gene expression of different cytokines beside all steps of viral growth cycle notably entry, replication and nucleic acid synthesis. The present review suggests a study on the possible effect on the expression of ACE-2 protein that has a role in the entry of COVID-19 to human cells. Surveillance studies are required on patients for close observations of any symptoms appearing during the intake of different therapeutic protocols that involve NSAIDs.

## Conflict of Interest

The authors declare that they have no conflicts interest.

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