



Prospective role of NSAIDs with antiviral properties for pharmacological management of postsurgical procedures during COVID-19

Firzan Nainu, PhD^a, Sukanto S. Mamada, MSc^a, Talha B. Emran, PhD^{b,c,*}

Dear Editor,

Almost 3 years since its first case report, coronavirus disease 2019 (COVID-19) remains one of the most discussed topics in the world. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, infects host cells, mainly in the respiratory tracts, via immediate attachment to the angiotensin-converting enzyme type 2 receptor at the surface of host cells^[1]. SARS-CoV-2-infected patients may then develop several symptoms, including fever, body pain, and malaise^[2,3]. Some of these symptoms can also develop after patients undergo surgical procedures^[4]. Indeed, during the early times of COVID-19 and even until now, surgical procedures face great challenges due to the high number of COVID-19 cases and possible viral transmission before, during, and after surgical procedures were taken^[5].

To manage fever and inflammatory-related symptoms, antipyretics, and analgesics, classified as NSAIDs, are commonly used^[6]. NSAID drugs act via the inhibition of arachidonic acid conversion to prostaglandins. This mechanism of action has been suggested to play a major role in the inhibition of pain sensation and resolution of inflammation^[7]. Apart from their desired pharmacological effects, some NSAIDs have been suggested to cause immunosuppression, and this has been a subject of scientific debate^[8]. In this correspondence piece, we would like to raise the awareness about the immunosuppressive effect of NSAIDs, which is quite debatable, as well as their documented antiviral activity against major viruses, including SARS-CoV-2. Evidence on these two seemingly unrelated pharmacological effects shall be critically assessed and carefully managed to achieve the best use of NSAIDs in the postsurgical management amid the emerging and re-emerging of viral infectious diseases.

How actually NSAIDs exert their immunosuppressive effect? Kazama *et al.*^[9] reported that immunosuppressive actions of

NSAIDs are associated with their ability to inhibit the delayed rectifier K⁺-channels (Kv1.3 channels) highly expressed in the T lymphocytes, which are pivotal for facilitating lymphocytes activation and proliferation. As a result, the immune response of T lymphocytes is suppressed. Pharmacologically, this inhibitory mechanism should be considered a novel strategy to block the emergence of cytokine storms in COVID-19 patients^[10]. The inhibition of lymphocyte activation might also be linked to the inhibition of p38 mitogen-activated protein kinases (MAPK)^[11,12]. This pathway is responsible for mediating several biological processes due to the various stress stimuli (e.g. microbes with their products and cytokines). In response to these stimuli, macrophages are activated followed by the activation of signaling pathways responsible for producing inflammatory mediators.

Of several pathways involved in inflammatory cascades, the MAPK pathways play a significant role^[11]. These pathways could induce nuclear factor- κ B activation, which is heavily involved in the process of inflammation and immune responses, including the production of proinflammatory cytokines, such as tumor necrosis factor- α ^[11,13]. It has also been demonstrated that p38 MAPK activation is closely linked to the expression of the COX-2 gene and stabilization of COX-2 posttranscription^[12]. It has long been noted that NSAIDs exert their anti-inflammatory action by blocking the activity of enzymes called cyclooxygenases. This enzyme is responsible for catalyzing the conversion of arachidonic acid to inflammatory mediators, including prostaglandins, followed by their binding to the appropriate receptors. This binding would eventually trigger inflammatory responses.

Several studies have reported NSAIDs' ability to disturb the production and action of cytokines and antibodies^[14–16]. In the current conditions, in the cases of COVID-19, the use of NSAIDs has been reported to dampen the excessive antibodies and cytokine responses^[15]. This use might be helpful given that in SARS-CoV-2 infection, the expression of COX-2 shows upregulation^[15]. Taken together, the use of analgesics/antipyretics/NSAIDs has been long accepted in alleviating the excessive inflammatory events which are often had by patients suffering from viral infections, including COVID-19. Furthermore, a rapid systematic review revealed that current evidence remains inadequate to support the assumption that NSAIDs have a negative impact on the adverse events, acute healthcare utilization, long-term survival, or quality of life in patients with COVID-19^[17]. Hence, the use of NSAIDs in the management of inflammation and pain-related symptoms may still clinically relevant during the times of COVID-19.

One of the worldwide priorities is to ensure effective antiviral agents against emerging and re-emerging viral diseases are available^[18]. To support this effort, researchers thrived to

^aDepartment of Pharmacy, Faculty of Pharmacy, Hasanuddin University, Makassar, Indonesia, ^bDepartment of Pharmacy, BGC Trust University Bangladesh, Chittagong and ^cDepartment of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, Dhaka, Bangladesh

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: Department of Pharmacy, BGC Trust University Bangladesh, Chittagong 4381, Bangladesh. E-mail address: talhabmb@bgctub.ac.bd (T.B. Emran).

Copyright © 2023 The Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

International Journal of Surgery (2023) 109:109–111

Received 19 October 2022; Accepted 16 November 2022

Published online 16 February 2023

<http://dx.doi.org/10.1097/JS9.000000000000101>

Table 1**List of NSAIDs with prospective antiviral properties against human viruses**

Drugs	Key findings	References
Antrafenine	Using in-silico analysis, antrafenine was shown to yield good antiviral activity against DENV-2 by targeting virus envelope glycoprotein	[19]
Aspirin	Aspirin produced no antiviral activity against DNA viruses (HSV-1 and Adeno-5). However, its antiviral effect can be seen against RNA viruses in the in-vitro setting: low activity against respiratory syncytial virus and high activity against influenza A H1N1 virus and human rhinoviruses	[20]
Indomethacin	Indomethacin demonstrated a great potency in reducing viral replication in both SARS-CoV-infected Vero and -infected A549 cells. Antiviral activity of indomethacin might not be mediated by cyclooxygenase blockage, viral infectivity, and blockage of either binding or entry of the virus. Instead, the antiviral effect of indomethacin might be related to its ability to inhibit viral protein synthesis	[21]
Mefenamic acid	In combination with ribavirin, mefenamic acid showed potent in-vitro and in-vivo antiviral activity against the chikungunya virus	[22]
Naproxen	Naproxen demonstrated its antiviral activity against influenza A virus (H1N1 and H3N2) in the in-vitro and in-vivo setting	[23]
Naproxen	In-vivo study in mice showed that naproxen halted the nuclear export of nucleoproteins of influenza A and B viruses leading to the inhibition of viral replication. This action is mediated by the ability of naproxen to directly bind to the viral nucleoprotein	[24]
Naproxen	Naproxen demonstrated antiviral properties against SARS-CoV-2 using in-silico (molecular docking analysis using Autodock Vina) and in-vitro (SARS-CoV-2-infected Vero E6 and HAE cells) approaches	[25]
Piroxicam	Piroxicam yielded a promising antiviral activity, in combination with azithromycin, in the treatment of SARS-CoV-2	[26]
Andrographolide, etanercept, adalimumab, infliximab, golimumab, olsalazine, myricetin, and ketoprofen	A network bioinformatics study using the AutoSeed program equipped with the AutoNet program to build the protein network showed that several analgesics, antipyretic and anti-inflammatory drugs had potencies against SARS-CoV-2	[27]
Lenalidomide, celecoxib, sulfasalazine, tenoxicam, meclofenamic acid, and loxoprofen	A meta-analysis approach proposed the potencies of several drugs to be further investigated as anti-SARS-CoV-2 indicated by a high negative tau score. Their antiviral activity might be related to their action on inhibiting cyclooxygenase-2 (COX-2). It has been demonstrated that COX-2 might have a role in mediating the entry of coronavirus ^[28] . Furthermore, another study demonstrated that COX-2 could limit the actions of antiviral cytokines. Thus, COX-2 inhibitors might play a significant role in enhancing the host antiviral immunity ^[29]	[28–30]

CC50, 50% cytotoxic concentration; COX-2, cyclooxygenase-2; DENV-2, dengue virus serotype 2; HAE cells, human airway epithelial cells; hpi, hours postinfection; HSV-1, human herpesvirus simplex virus type 1.

discover new antiviral candidates as well as repurpose the already available drugs. To date, several NSAIDs have been shown to yield antiviral properties, with promising effects against certain human viruses, including SARS-CoV-2 (Table 1). Although research looking at the antiviral activities of NSAIDs is still ongoing, there is a potential path to be taken for future disease management in the case of viral infection. Naproxen, for example, was demonstrated as a potent antiviral against both influenza A virus and SARS-CoV-2^[23,25]. In addition to naproxen, one of the most commonly used NSAIDs, paracetamol, has been demonstrated to alter the expression of genes involved in the entry of SARS-CoV-2 as well as arachidonic acid metabolism^[31]. Furthermore, another group of investigators have also reported the antiviral potential of indomethacin against SARS-CoV^[21] and SARS-CoV-2^[32] in the in-vitro settings, adding more prospective antiviral agents in the list. In addition to their promising effect against SARS-CoV-2, some NSAIDs have also been shown active against several human viruses, including dengue virus, chikungunya virus, and human rhinoviruses (Table 1).

In conclusion, relevant evidence suggested that certain NSAIDs with their combinatorial anti-inflammatory and antiviral effects could provide more efficient results in alleviating the respiratory distress symptoms and hyperinflammatory responses caused by COVID-19. Such pharmacological approach shall bring tremendous efficacy for the patients suffering from COVID-

19-related cytokine storm or similar symptoms caused by other viral diseases.

Ethical approval

Not applicable.

Sources of funding

None.

Authors' contribution

F.N. and T.B.E. designed the study. F.N. and S.S.M. wrote the first draft. F.N., S.S.M., and T.B.E. updated the manuscript. F.N., S.S.M., and T.B.E. reviewed the final draft. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Conflicts of interest disclosure

The authors declare that they have no financial conflicts of interest with regard to the consent of this report.

Research registration unique identifying number (UIN)

None.

Guarantor

Firzan Nainu and Talha Bin Emran.

Provenance and peer review

Not commissioned, internally peer-reviewed.

Acknowledgments

The authors are thankful to their parent institutions.

References

- [1] Hoffmann M, Kleine-Weber H, Schroeder S, *et al.* SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181:271–80.e278.
- [2] Israfil SMH, Sarker MMR, Rashid PT, *et al.* Clinical characteristics and diagnostic challenges of COVID-19: an update from the global perspective. *Front Public Health* 2020;8:567395.
- [3] Ng SL, Ong YS, Khaw KY, *et al.* Focused review: potential rare and atypical symptoms as indicator for targeted COVID-19 screening. *Medicina* 2021;57:189.
- [4] Bourget-Murray J, Heard BJ, Bansal R, *et al.* Postoperative fever in the time of COVID-19. *Can J Surg* 2020;63:E231–2.
- [5] Al-Jabir A, Kerwan A, Nicola M, *et al.* Impact of the coronavirus (COVID-19) pandemic on surgical practice – part 1. *Int J Surg* 2020;79:168–79.
- [6] Zhou Q, Zhao S, Gan L, *et al.* Use of non-steroidal anti-inflammatory drugs and adverse outcomes during the COVID-19 pandemic: a systematic review and meta-analysis. *EClinicalMedicine* 2022;46:101373.
- [7] Bertolini A, Ottani A, Sandrini M. Dual acting anti-inflammatory drugs: a reappraisal. *Pharmacol Res* 2001;44:437–50.
- [8] Pergolizzi JV Jr, Varrassi G, Magnusson P, *et al.* COVID-19 and NSAIDs: a narrative review of knowns and unknowns. *Pain Ther* 2020;9:353–8.
- [9] Kazama I, Maruyama Y, Murata Y. Suppressive effects of nonsteroidal anti-inflammatory drugs diclofenac sodium, salicylate and indomethacin on delayed rectifier K⁺-channel currents in murine thymocytes. *Immunopharmacol Immunotoxicol* 2012;34:874–.
- [10] Kazama I. Targeting lymphocyte Kv1. 3-channels to suppress cytokine storm in severe COVID-19: can it be a novel therapeutic strategy? *Drug Discov Ther* 2020;4:143–4.
- [11] Kaminska B. MAPK signalling pathways as molecular targets for anti-inflammatory therapy – from molecular mechanisms to therapeutic benefits. *Biochim Biophys Acta* 2005;1754:253–62.
- [12] Paccani SR, Boncristiano M, Olivieri C, *et al.* Nonsteroidal anti-inflammatory drugs suppress T-cell activation by inhibiting p38 MAPK induction. *J Biol Chem* 2002;277:1509–3.
- [13] Giuliani C, Bucci I, Napolitano G. The role of the transcription factor nuclear factor-kappa B in thyroid autoimmunity and cancer. *Front Endocrinol* 2018;9:471.
- [14] Bancos S, Bernard MP, Topham DJ, *et al.* Ibuprofen and other widely used non-steroidal anti-inflammatory drugs inhibit antibody production in human cells. *Cell Immunol* 2009;258:18–28.
- [15] Chen JS, Alfajaro MM, Chow RD, *et al.* Nonsteroidal anti-inflammatory drugs dampen the cytokine and antibody response to SARS-CoV-2 infection. *J Virol* 2021;95:e00014–00021.
- [16] Liu K, Yu J, Xia Y, *et al.* The combination of ciprofloxacin and indomethacin suppresses the level of inflammatory cytokines secreted by macrophages in vitro. *Chin J Traumatol* 2022;25:379–88.
- [17] WHO. The use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with COVID-19/WHO; 2020. Accessed October 16, 2022. [https://www.who.int/news-room/commentaries/detail/the-use-of-non-steroidal-anti-inflammatory-drugs-\(nsaids\)-in-patients-with-covid-19](https://www.who.int/news-room/commentaries/detail/the-use-of-non-steroidal-anti-inflammatory-drugs-(nsaids)-in-patients-with-covid-19)
- [18] Meganck RM, Baric RS. Developing therapeutic approaches for twenty-first-century emerging infectious viral diseases. *Nature Med* 2021;27:401–10.
- [19] Montes-Grajales D, Puerta-Guardo H, Espinosa DA, *et al.* In silico drug repurposing for the identification of potential candidate molecules against arboviruses infection. *Antiviral Res* 2020;173:104668.
- [20] Glatthaar-Saalmüller B, Mair KH, Saalmüller A. Antiviral activity of aspirin against RNA viruses of the respiratory tract-an in vitro study. *Influenza Other Respir Viruses* 2017;11:85–92.
- [21] Amici C, Di Caro A, Ciucci A, *et al.* Indomethacin has a potent antiviral activity against SARS coronavirus. *Antivir Ther* 2006;11:1021–30.
- [22] Rothan HA, Bahrani H, Abdulrahman AY, *et al.* Mefenamic acid in combination with ribavirin shows significant effects in reducing chikungunya virus infection in vitro and in vivo. *Antiviral Res* 2016;127:50–6.
- [23] Lejal N, Tarus B, Bouguyon E, *et al.* Structure-based discovery of the novel antiviral properties of naproxen against the nucleoprotein of influenza A virus. *Antimicrob Agents Chemother* 2013;57:2231–42.
- [24] Zheng W, Fan W, Zhang S, *et al.* Naproxen exhibits broad anti-influenza virus activity in mice by impeding viral nucleoprotein nuclear export. *Cell Rep* 2019;27:1875–85.
- [25] Terrier O, Dilly S, Pizzorno A, *et al.* Antiviral properties of the NSAID drug naproxen targeting the nucleoprotein of SARS-CoV-2 coronavirus. *Molecules* 2021;26:2593.
- [26] Mostafa A, Kandeil A, Y AMME, *et al.* FDA-approved drugs with potent in vitro antiviral activity against severe acute respiratory syndrome coronavirus 2. *Pharmaceuticals (Basel)* 2020;13:443.
- [27] Li X, Yu J, Zhang Z, *et al.* Network bioinformatics analysis provides insight into drug repurposing for COVID-19. *Med Drug Discov* 2021;10:100090.
- [28] Raaben M, Einerhand AW, Taminiau LJ, *et al.* Cyclooxygenase activity is important for efficient replication of mouse hepatitis virus at an early stage of infection. *Virol J* 2007;4:1–5.
- [29] Kirkby NS, Zaiss AK, Wright WR, *et al.* Differential COX-2 induction by viral and bacterial PAMPs: Consequences for cytokine and interferon responses and implications for anti-viral COX-2 directed therapies. *Biochem Biophys Res Commun* 2013;438:249–56.
- [30] Loganathan T, Ramachandran S, Shankaran P, *et al.* Host transcriptome-guided drug repurposing for COVID-19 treatment: a meta-analysis based approach. *PeerJ* 2020;8:e9357.
- [31] Khirfan F, Jarrar Y, Al-Qirim T, *et al.* Analgesics induce alterations in the expression of SARS-CoV-2 entry and arachidonic-acid-metabolizing genes in the mouse lungs. *Pharmaceuticals* 2022;15:696.
- [32] Xu T, Gao X, Wu Z, *et al.* Indomethacin has a potent antiviral activity against SARS CoV-2 in vitro and canine coronavirus in vivo. *bioRxiv* 2020:1–12.