Received: 10 September 2022 | Accepted: 10 November 2022

DOI: 10.1111/bph.15989

PERSPECTIVE

Hypothesis: Efficacy of early treatments with some NSAIDs in COVID-19: Might it also depend on their direct and/or indirect zinc chelating ability?

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The present work argues for the involvement of the zinc chelating ability of some non-steroidal anti-inflammatory drugs as an additive mechanism able to increase their efficacy against COVID-19.

KEYWORDS
glutathione, non-steroidal anti-inflammatory drugs, paracetamol, renin-angiotensin system, severe acute respiratory syndrome coronavirus 2, zinc chelation, zinc metalloproteases

1 | INTRODUCTION

COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, a disease for which several immunological and pharmacological treatments have been tried. Besides mass vaccination, early use of some pharmacological treatments including non-steroidal anti-inflammatory drugs (NSAIDs) has been shown to exert some protective effects against COVID-19 (Consolaro et al., 2022; Cosentino et al., 2022; Fazio et al., 2021; Perico et al., 2022; Suter et al., 2021; Zamai & Rocchi, 2022). In this regard, a recent study reported that the rate of prescriptions of NSAIDs or paracetamol for symptomatic relief differs between non-hospitalised and hospitalised patients (Whittaker et al., 2021). Paracetamol prescriptions post-COVID-19 had the greater increase compared with 12 months before infection in hospitalised patients, suggesting that among them, there were more people used to take paracetamol for pain relief. Differently, NSAIDs, followed by opioids, were the most common drugs prescribed in COVID-19 non-hospitalised persons after COVID-19 compared with the period 12 months previously (Whittaker et al., 2021), indicating that NSAIDs were preferred to opioids and paracetamol in the cohort of individuals managed in the community that did not require hospital admission. These observations may possibly account for relatively low percentages (only ~6%) of hospitalised patients taking NSAIDs before admission to hospital for pain relief during the first phase of infection (Drake et al., 2021), as the majority of them likely used paracetamol or opioids for symptomatic relief of COVID-19 symptoms before hospital admission. Correlations between (some) NSAID administration and protection from severe COVID-19 and/or paracetamol administration and increased hospitalisation can therefore be hypothesised. Indeed, NSAIDs have been found effective in the early phases of the disease and especially in some 'responder' patients, whereas the combination with other medications tailored to individual symptom progression and medical history was also necessary in some other patients (Consolaro et al., 2022; Fazio et al., 2021; Suter et al., 2021). In this regard, two observational studies have shown that NSAID treatment with celecoxib/nimesulide (~70%) or with aspirin (~10%) started early at home and associated if necessary with antibiotics (azithromycin ~50%), corticosteroids (~30%) and/or anticoagulants markedly reduced the risk of hospitalisation compared to a 'control' treatment with paracetamol (~60%) or with ketoprofen/ibuprofen (~10%) (Consolaro et al., 2022; Suter et al., 2021). Therefore, symptomatic treatments differ in 'protecting' from severe COVID-19, with more selective cyclooxygenase-2 (COX-2) inhibitors (celecoxib/nimesulide) showing better efficacy than other symptomatic drugs (Consolaro et al., 2022; Suter et al., 2021). In line with this hypothesis, another paper showed that celecoxib could both prevent disease progression and promote recovery from COVID-19, whereas ibuprofen was less effective (Hong et al., 2020). Protective effects against COVID-19 were also shown for indomethacin or aspirin (Fazio et al., 2021; Perico et al., 2022; Ravichandran et al., 2022). Despite an overlapping mechanism of action, some other NSAIDs, such as ketoprofen, were not shown to be effective against COVID-19

Abbreviations: GSH, glutathione; LCFAs, long-chain fatty acids; NAC, *N*-acetylcysteine.

(Consolaro et al., 2022; Suter et al., 2021), suggesting that the mechanism(s) of NSAID protection might not exclusively depend on their COX-inhibiting activity. Differences in COX-independent mechanisms among these compounds have already been described (Tegeder et al., 2001). Because additional effects may affect either efficacy or toxicity, these may have therapeutic consequences depending on a specific disease and/or patient, possibly accounting for weak associations between NSAID use and COVID-19 protection (Reese et al., 2022; Zhou et al., 2022). Therefore, the underlying mechanism(s) leading to different COVID-19 outcomes depending on the NSAID used should be elucidated.

2 | SARS-COV-INDUCED HYPERACTIVITY OF ANGIOTENSIN-CONVERTING ENZYME 2 (ACE2) ZINC METALLOPROTEASE AND COVID-19 SEVERITY: THE POSSIBLE ROLE OF PHOSPHOLIPASE A2 (PLA2)

Unlike HCoV-NL63, SARS-CoV binding to cell surface ACE2 has been shown to induce both ADAM17-mediated shedding of an enzymatically active ACE2 and severe acute respiratory syndrome (SARS) (Glowacka et al., 2010; Haga et al., 2008; Lambert et al., 2005; Lartey et al., 2022; Yeung et al., 2021), raising the possibility that systemic ACE2 hyperactivity may participate in COVID-19 pathogenesis (Montanari et al., 2021; Zamai, 2020, 2021; Zanza et al., 2021). As a consequence of SARS-CoV spike binding, ACE2 expressed on endothelial cells would be down-modulated and an excess of active ACE2 released in circulation (Fagyas et al., 2022; Montanari et al., 2021; Zamai, 2020). Indeed, spike protein alone as well as the SARS-CoV viral infection have been shown to both down-modulate ACE2 surface expression and damage endothelium in in vivo animal models (Lei et al., 2021; Nuovo et al., 2021), suggesting that the renin–angiotensin system dysregulation induced by SARS-CoV spike binding independently of viral infection may play a central role in COVID-19. In this regard, both COVID-19 severity and pre-existing comorbidities associated with severe COVID-19 (e.g., male sex, age, cardiopathies, hypertension and diabetes) are characterised by an increased activity of circulating ACE2 (Anguiano et al., 2015; Epelman et al., 2009; Fagyas et al., 2022; Montanari et al., 2021; Nagy et al., 2021; Ortiz-Perez et al., 2013; Patel et al., 2021; Pucci et al., 2021; Ramchand et al., 2018; Reindl-Schwaighofer et al., 2021; Soro-Paavonen et al., 2012; Úri et al., 2014, 2016; Valle Martins et al., 2021; van Lier et al., 2021; Walters et al., 2017; Zamai, 2020, 2021), suggesting that an elevated baseline ACE2 activity (further up-regulated by SARS-CoV infection) can predispose to severe COVID-19. Indeed, hyperactivation of pathways downstream of ACE2, that is, angiotensin-(1–7)/Mas receptor and/or angiotensin-(1–9)/angiotensin type 2 (AT_2) receptor, has been shown to promote various positive feedback loops, leading to COVID-19-like manifestations, and inhibition of ACE2 and/or ADAM17 zinc metalloproteases through zinc-chelating agents has been proposed as a therapeutic approach for COVID-19 treatment (Montanari et al., 2021; Zamai, 2020, 2021). Among other consequences, stimulation of the Mas receptor or AT_2 receptor pathways induces PLA2 activation, arachidonic acid (AA) release, COX activation and prostaglandin (PG) production (Andreatta-van Leyen et al., 1993; Jacobs & Douglas, 1996; Jaiswal et al., 1991, 1992, 1993; Liao et al., 2011; Lokuta et al., 1994; Muthalif et al., 1998; Zhu et al., 1998).

In this regard, PLA2 has been shown to play a critical role in murine models of either virus-independent acute/adult respiratory distress syndrome (ARDS) or age-related susceptibility to SARS-CoV-1 (Nagase et al., 2000; Vijay et al., 2015). Interestingly, only patients with ARDS (requiring mechanical ventilation or oxygen) were protected from COVID-19-induced mortality by dexamethasone administration (RECOVERY Collaborative Group et al., 2021). Knowing that corticosteroids can inhibit PLA2 via induction of lipocortin proteins (Parente, 2001; Solito & Parente, 1989; Vishwanath et al., 1993), a possible mechanism of action of dexamethasone can be hypothesised.

It is known that phospholipases, by hydrolysing phospholipids, release long-chain fatty acids (LCFAs) such as AA and linoleic acid, which are metabolised by COXs (COX-1 and COX-2) to inflammatory/pro-thrombotic mediators, including PGs (Pérez-Torres et al., 2021; Vijay et al., 2015). Interestingly, AA and linoleic acid in plasma and PGE2 in urine have been shown to strongly increase in severe COVID-19 patients, whereas albumin (known to sequester a variety of LCFAs and, thus, reduce their bioavailability in plasma) has been shown to strongly decrease (Coverdale et al., 2019; Hong et al., 2020; Montanari et al., 2021; Nguyen et al., 2021; Pérez-Torres et al., 2021; Zamai, 2020, 2021). Moreover, up-regulation of nuclear factor-κB (NF-κB) transcription factor and downstream-regulated genes including PLA2 and COX-2 characterise early stages of COVID-19 (Yan et al., 2021). Of note, NF-κB transcription, COX-2 expression and PGE2 production can be up-regulated by LCFAs (Fang et al., 2009; Meade et al., 1999). Among the LCFAs, linoleic acid, when administered to endothelial cells, has been shown to disrupt endothelial barrier integrity concomitantly with NF-κB up-regulation, AA release, glutathione (GSH) reduction and lipid peroxidation (Hennig et al., 1996, 2000), suggesting that an excess of LCFAs may induce oxidative stress to endothelial cells (Hennig et al., 1996, 2000); however, the degree of fatty acid unsaturation determining the susceptibility to lipid peroxidation of LFCAs and the endothelial dysfunction were not correlated, suggesting the involvement of mechanisms that participate to establish positive feedback loops downstream of ACE2 activity other than oxidative stress (Fang et al., 2009; Hennig et al., 2000).

3 | ACE2 AND ADAM17 ZINC METALLOPROTEASE INHIBITION BY ZINC-CHELATING AGENTS AS A THERAPEUTIC STRATEGY AGAINST SEVERE COVID-19

LCFAs have been shown to cause the release of Zn^{2+} from albumin, the major 'storage reservoir'/carrier of plasma zinc (Coverdale et al., 2019). Therefore, COVID-19-induced release of LCFAs and hypoalbuminaemia can temporarily increase free Zn^{2+}, which can be easily imported by endothelial cells and available for newly synthesised ACE2 and ADAM17 (that mediates ACE2 shedding) zinc

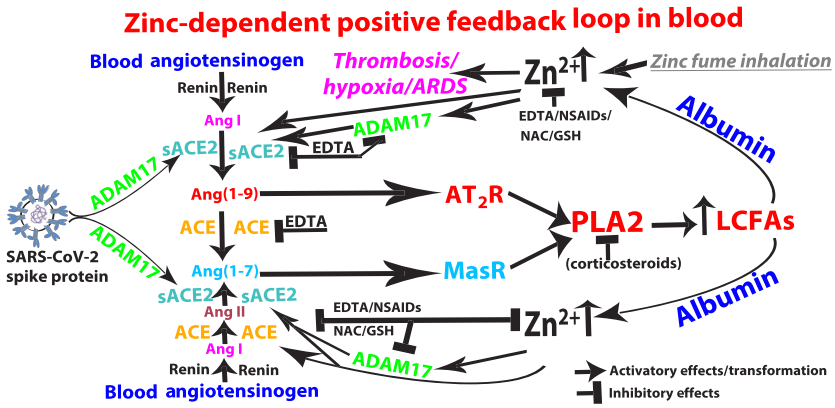

FIGURE 1 Putative zinc-dependent positive feedback loop mediated by the renin–angiotensin system (RAS)–phospholipase A2 (PLA2) axis activation in COVID-19 and its inhibition through zinc-chelating agents. ACE, angiotensin-converting enzyme; Ang, angiotensin; ARDS, acute/adult respiratory distress syndrome; AT_2R, angiotensin type 2 receptor; EDTA, ethylenediaminetetraacetic acid; GSH, reduced glutathione; LCFAs, long-chain fatty acids; MasR, mas receptor; NAC, *N*-acetylcysteine; NSAIDs, non-steroidal anti-inflammatory drugs; sACE2, soluble angiotensin-converting enzyme 2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2 (for reference, see text). Arrows, activatory effects/transformation; T, inhibitory effects

metalloproteases. This hypothetical mechanism would lead to further increased activity not only of circulating ACE2 but also of downstream PLA2 (Andreatta-van Leyen et al., 1993; Jacobs & Douglas, 1996; Lokuta et al., 1994; Muthalif et al., 1998; Zhu et al., 1998), finally establishing a positive feedback loop that further increases LCFAs and consequently bioavailable Zn^{2+} (see Figure 1). Because high concentrations of Zn^{2+} have been shown to activate ACE2 (and angiotensin-converting enzyme [ACE]) zinc metalloprotease (Anguiano et al., 2015), a similar positive feedback loop, albeit SARS-CoV-2 independent, might be also induced by zinc fume inhalation, which has been shown to cause both elevated plasma zinc levels and ARDS with COVID-19-like lung radiographic and angiographic pictures (Hjortsø et al., 1988; Xie et al., 2017). In particular, widespread occlusion of the pulmonary arteries and marked endothelial cell injury resembling COVID-19 suggest the occurrence of thrombotic events, which were possibly mediated by increase of free zinc (seeMontanari et al., 2021; Zamai, 2020, 2021).

Altogether, the hypothesised pathophysiological mechanism of COVID-19 is expected to shift zinc from albumin-bound to albumin-unbound species (such as free Zn^{2+} and/or ACE2-bound zinc) in plasma. Indeed, zinc/albumin ratio has been recently found to be significantly higher in COVID-19 patients than in diabetic patients and healthy subjects (manuscript in preparation), providing further reason for the therapeutic use of zinc-chelating agents able to inhibit ACE2 and ADAM17 zinc metalloproteases and thrombosis for severe COVID-19. In this regard, the anticoagulant/metal chelator ethylenediaminetetraacetic acid (EDTA), which is able to inhibit both ACE2 and ADAM17 zinc metalloproteases (Anguiano et al., 2015; Chen et al., 2007; Peng et al., 2010; Towler et al., 2004; Vickers et al., 2002), has been proposed as an anti-COVID-19 agent (Montanari et al., 2021; Zamai, 2020, 2021). Moreover, inhibition of zinc-dependent enzymes through zinc displacement by bismuth-based drugs was shown to be effective in a COVID-19 hamster model (Yuan et al., 2020), suggesting the efficacy of targeting zinc-dependent pathways. Finally, inhibition of ADAM17 has been shown to be effective to prevent COVID-19-like manifestations in a mouse model (Lartey et al., 2022), indicating the crucial role of this zinc metalloprotease.

4 | DIRECT AND INDIRECT ZINC CHELATING PROPERTIES OF NSAIDS AND RESERVE OF GSH CORRELATE WITH PROTECTION FROM SEVERE COVID-19

Interestingly, most of the NSAIDs shown to reduce risk of hospitalisation (nimesulide, aspirin and indomethacin) form complexes with zinc, and nimesulide complexes have higher stability than ibuprofen complexes (Baslas et al., 1979; Chohan et al., 2002; Fini et al., 2001; Kaur et al., 2013; Yoshikawa et al., 2011). Moreover, celecoxib forms water-insoluble complexes with $metal^{2+}$ (Vadivel & Korgaonkar, 2018), and several antibiotics including azithromycin and tetracyclines can chelate zinc; the last has also been shown to inhibit matrix metalloproteinases (Arayne et al., 2014; Dalhoff, 2021). Similarly, *N*-acetylcysteine (NAC) and its metabolites, cysteine and GSH, can complex zinc (Brumas et al., 1992; Chen & Liao, 2003; Krezel et al., 2003). Notably, NAC has been shown to protect from endothelial cell damage induced by SARS-CoV-2 spike protein in vitro (Lei et al., 2021), and both NAC and GSH can inhibit ADAM17 activity (Stolarczyk et al., 2018). More importantly, the combination of NAC with a bismuth-based drug via an oral route exhibits anti-SARS-CoV-2 potency in a hamster model (Li et al., 2022). However, only NAC is expected to functionally inhibit ACE2 (Li et al., 2022), whereas bismuth might affect ADAM17 activity interfering with its cysteine-rich domain. Interestingly, NAC treatment works not only against COVID-19 but also against both zinc fume inhalation eliminating plasma zinc and paracetamol toxicity by replenishing GSH (Brumas et al., 1992; Hjortsø et al., 1988; Sestili & Fimognari, 2020). On the other hand, GSH depletion is induced by elevated extracellular zinc concentrations and ketoprofen or paracetamol treatments and correlates with severe COVID-19/ARDS (Brumas et al., 1992; Chen & Liao, 2003; Micheli et al., 1992; Sestili & Fimognari, 2020). Because GSH depletion exacerbates zinc-induced cytotoxicity (Chen & Liao, 2003), it raises the possibility that ACE2 up-regulation, leading to COVID-19 worsening (Patel et al., 2021) and possibly to increased Zn^{2+} availability, might be further increased by paracetamol- or ketoprofen-mediated GSH depletion. Anti-oxidative activities of NAC or GSH are thought to prevent LCFA-induced vascular endothelial damage and zinc cytotoxicity

(Chen & Liao, 2003; Hennig et al., 1996; Zhou et al., 2013); however, other antioxidants different from NAC and GSH fail to protect from zinc cytotoxicity, suggesting that NAC and GSH may also act and protect via zinc chelation (Chen & Liao, 2003). Intriguingly, structurally and functionally different drugs such as celecoxib, azithromycin, tetracyclines, EDTA, hydroxychloroquine and NAC share ability to both sequestrate/chelate Zn^{2+}/metal^{2+} and alleviate rheumatoid arthritis (Bamonti et al., 2011; Batooei et al., 2018; O'Dell et al., 2001; Vadivel & Korgaonkar, 2018; Xue et al., 2014; Zhang et al., 2022), suggesting that their ability to prevent inflammation in rheumatoid arthritis and possibly in COVID-19 may be through multiple mechanisms including zinc chelation and/or GSH replenishment. In this regard, Wong et al. demonstrated that current use of NSAIDs in individuals with rheumatoid arthritis/osteoarthritis was associated with a lower risk of COVID-19-related death, COX-2-specific inhibitors being the most effective drugs (Wong et al., 2021). Moreover, celecoxib, but not nimesulide and aspirin, has been shown to increase intestinal GSH levels in a rat model (Nair et al., 2006), and azithromycin administration was found to significantly decrease the glutathione disulfide (GSSG)/GSH ratio in airway cells consistent with its anti-inflammatory properties possibly through NF-κB inhibition (Bergamini et al., 2009).

Altogether, the present work suggests that symptomatic treatments of COVID-19 can exert multiple ('therapeutic' or adverse) effects, some of these effects may be mediated by mechanisms of direct metal/zinc chelation and/or indirect GSH depletion/replenishment. Differences in these types of 'additive' mechanisms may account for respective hospitalisation and consequent death rates between paracetamol (or ketoprofen) and some NSAIDs, such as COX-2 inhibitors. However, more investigation to validate the effectiveness of COX-2 inhibitors in protecting from severe COVID-19, possibly in part through zinc chelation and/or GSH replenishment, is needed.

4.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22 (Alexander, Christopoulos et al., 2021; Alexander, Fabbro, et al., 2021).

ACKNOWLEDGEMENTS

I have to thank Barbara di Giacomo and Philip Man Lung Yeung for their suggestions and encouragement. I hope that this work may help in facing future pandemic waves.

CONFLICT OF INTEREST

The author declares no competing interests.

AUTHOR CONTRIBUTION

L.Z. conceived and wrote the article and read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article because no new data were created or analysed in this study.

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How to cite this article: Zamai, L. (2023). Hypothesis: Efficacy of early treatments with some NSAIDs in COVID-19: Might it also depend on their direct and/or indirect zinc chelating ability? *British Journal of Pharmacology*, *180*(3), 279–286. https://doi.org/10.1111/bph.15989