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Review Article

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MEFENAMIC ACID A POTENTIAL TRANSMEMBRANE SERINE PROTEASE 2 INHIBITOR IN THE TREATMENT OF COVID-19

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ABSTRACT

COVID-19 (coronavirus disease 2019) is a Pandemic of concern, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). As of now, there is no known effective pharmaceutical or other medicine available for cure or prevention of COVID-19. In this review, based on the current understanding of the disease and the structure of novel Coronavirus SARS-CoV-2, SARS-CoV and other human viruses, is has been observed that Mefenamic Acid, an anti-inflammatory medicine, of having some role as an anti-viral medicine also. It can be used along with different anti-viral drugs being tried for the treatment of COVID-19. Since it is also an anti-pyretic, its main role may be of bringing down the fever but its action as an anti-viral, as a supportive medicine can very useful. Clinical trials with this concept in mind can be started immediately at the Centres dedicated for treatment of COVID-19.

KEYWORDS: COVID-19; SARS-CoV-2; Mefenamic acid, serine protease inhibitor, NLRP3 inflammasome.

INTRODUCTION

Mefenamic acid is one of the oldest NSAIDS (Nonsteroidal Anti-inflammatory Drugs), introduced into the market in 1967 for mild to moderate pain and for primary dysmenorrhea.

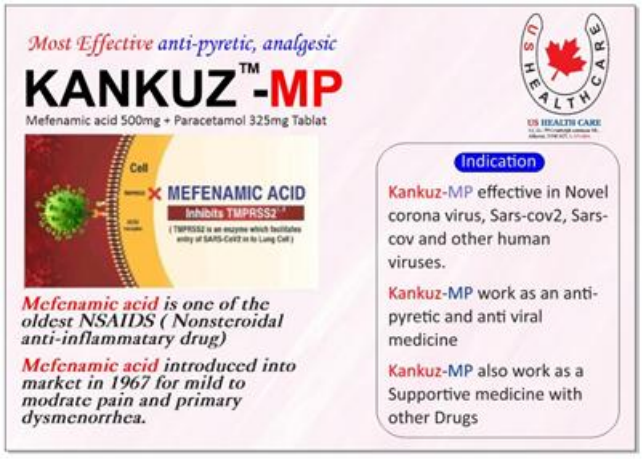


Figure-1: Mefenamic acid in formulation [KANKUZ-MP].

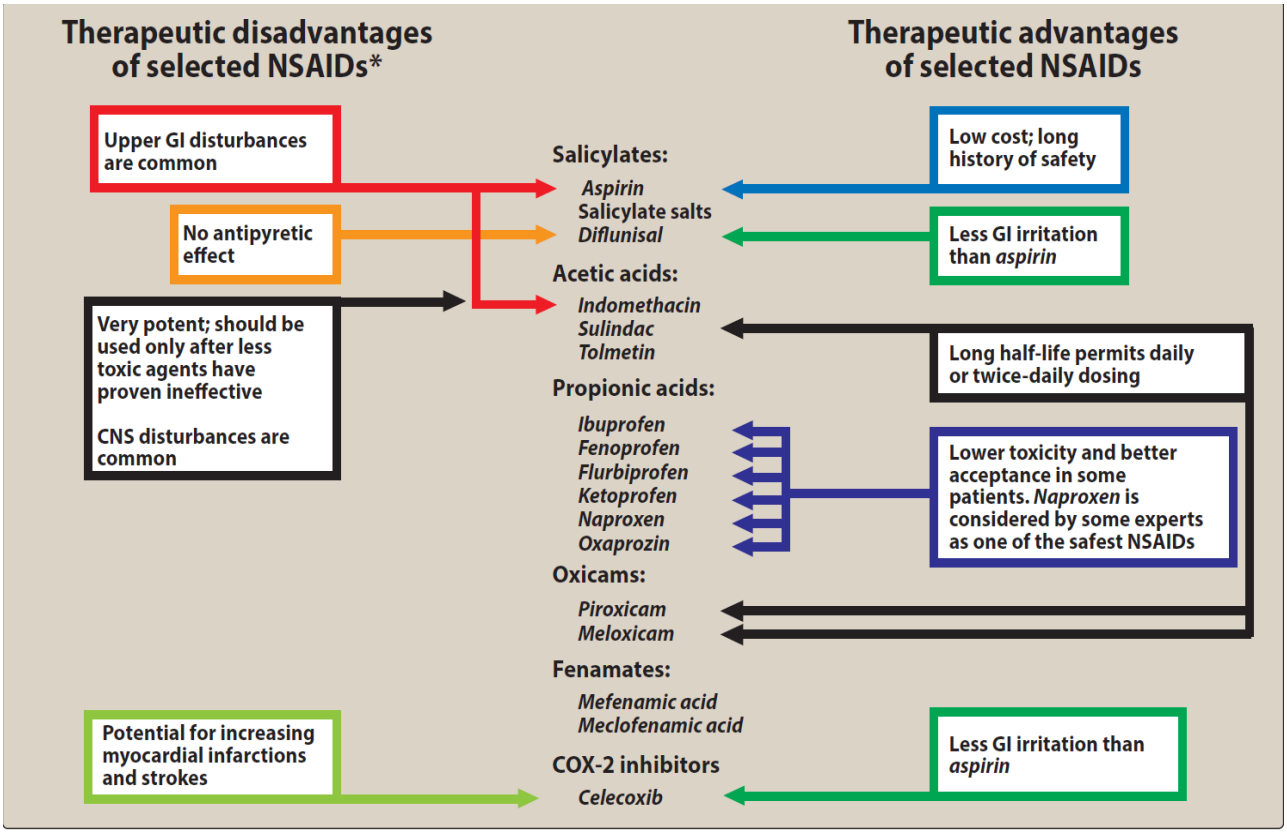
IUPAC: 2-(2,3-dimethylphenyl)aminobenzoic acid. Formula: $C_{15}H_{15}NO_2$, Molar mass: 241.290 g·mol^{-1} Chemically Mefenamic acid [CAS: 61-68-7] belongs to N-arylanthranilic acid (Fenamates) in which second aromatic ring is connected to the main aromatic carboxylic acid containing ring through a secondary amine linkage. As the result of this structural feature, this

class of NSAIDS appears to have lower risk of causing GI irritation.[1,2]

Use: Mefenamic acid is used to treat pain and inflammation in rheumatoid arthritis and osteoarthritis, postoperative pain, acute pain including muscle and back pain, toothache and menstrual pain, as well as being prescribed for menorrhagia. There is evidence that supports the use of mefenamic acid for perimenstrual migraine headache prophylaxis, with treatment starting two days prior to the onset of flow or one day prior to the expected onset of the headache and continuing for the duration of menstruation. Mefenamic acid is recommended to be taken with food.

Mechanism of action: Mefenamic acid is a non-selective COX inhibitor. It inhibits Cyclooxygenase enzymes and thus release of various inflammatory mediators such as prostaglandins (PG), thromboxane (TXA2) etc are blocked, and thus anti-inflammatory as well as analgesic effects are produced.

Indications-Analgesic, dysmenorrhea, arthritis.
Side effects: Diarrhoea is the most important dose related side effect. Epigastric distress. Gut bleeding. Skin rashes. Dizziness, and other CNS related complications. Haemolytic anaemia: rare but serious complication.[3,4]



Summary of nonsteroidal anti-inflammatory agents (NSAIDs). GI = gastrointestinal; CNS = central nervous system; COX-2 = cyclooxygenase-2. *As a group, with the exception of *aspirin*, these drugs may have the potential to increase risk of myocardial infarction and stroke.

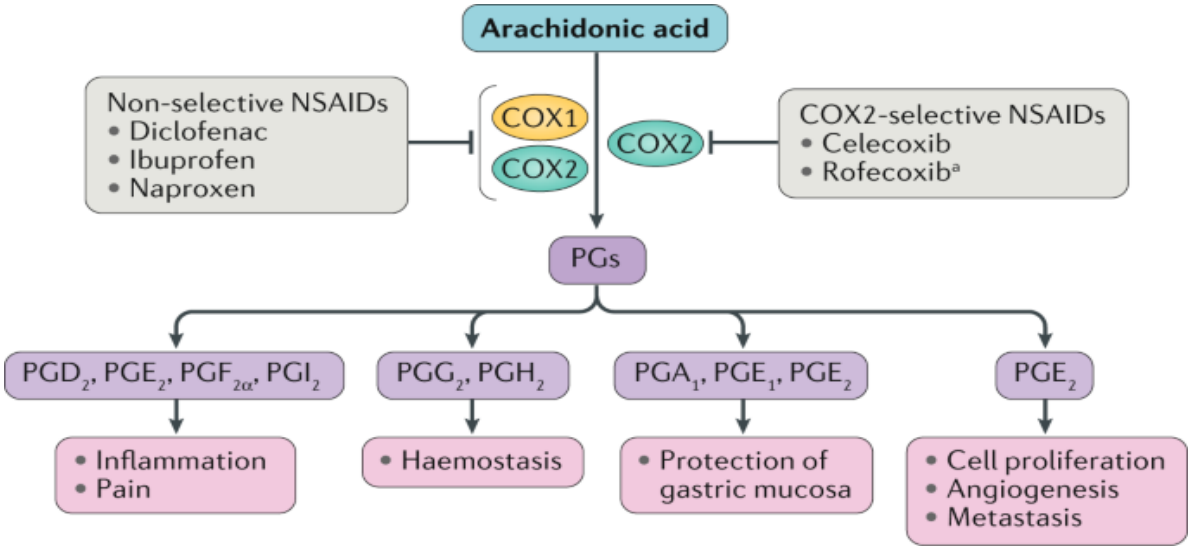


Figure-2: NSAID & Pain mediators.

ACE2 receptors: ACE2 is a protein found on the surface of many cell types. It is an enzyme that generates small proteins – by cutting up the larger protein angiotensinogen– that then go on to regulate functions in the cell. ACE2 is present in many cell types and tissues including the lungs, heart, blood vessels, kidneys, liver and G.I tract. It is present in epithelial cells which line certain tissues and create protective barriers. ACE2 receptors and viral infection: ACE2 receptors plays important role in viral infections: Using the spike-like protein on its surface virus such as binds to ACE2-like a key being inserted into a lock. Which is prior to entry and infection of cells. Hence, ACE2 that causes infection in our body.

Correlation of ACE2 receptor with viral infection and Mefenamic acid. As we have seen, ACE2 receptors plays important role in viral infections and Acts as a cellular doorway-a receptor-for the virus to enter in human cells.

Correlation of ACE2 and Mefenamic acid: Mefenamic acid have no direct effect on ACE2 receptor, but it could be beneficial in viral infection and have indirect effect on viral infection. Novel corona virus-induced NLRP3 Inflammasome activation: A potent Drug Target in treatment of COVID-19. Novel corona virus encodes ion-channel proteins called viroporins. These viroporins, via mechanisms such as lysosomal disruption and ion-redistribution in the intracellular environment, activate the innate immune signalling receptor NLRP3 (NOD-, LRR-and pyrin domain- containing 3) inflammasome. This leads to production of inflammatory cytokines such as interleukin IL-1ß, IL-6, TNF etc. This causing tissue inflammation during respiratory illness caused by CoV infection. Due to this important role in triggering inflammatory response to infection, the NLRP3 inflammasome appears to be potential drug target in treatment of COVID -19, caused by virus - SARS-COV-2.[5,6]

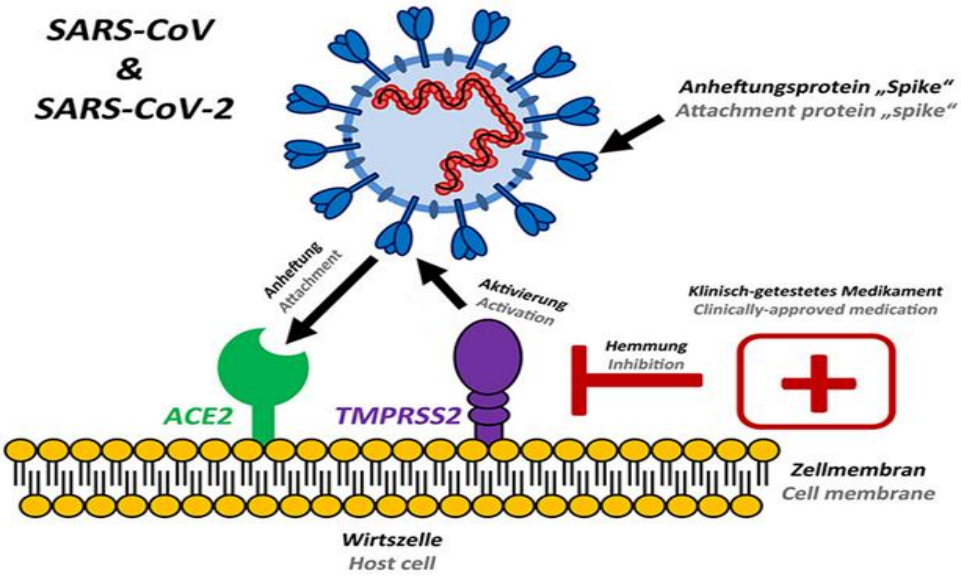


Figure-3: TMPRSS2 action on ACE2.

Inhibition of NLRP3 by Mefenamic acid. NSAIDs is a group of anti-inflammatory drugs inhibiting the COX enzymes in the synthesis PGs and other mediators and widely used for the treatment of pain and inflammation. Studies have shown that, unlike other NSAIDs, Fenamates (Mefenamic acid) selectively inhibits NLRP3 Inflammasome and IL-1ß release via inhibiting the membrane volume-regulated anion (Cl^-) channel, independent of its COX-1 mediated anti- inflammatory activity. Mefenamic acid and viral replication. In agreement with these findings Mefenamic acid was observed to have considerable activity against viral replication, and combination of Ribavirin together with Mefenamic acid was shown to be effective in reducing viral yield in cells infected with a positive sense RNA genome chikungunya virus.[7,8]

What is TMPRSS2? Transmembrane serine protease 2 (TMPRSS2) is a cell surface protein primarily expressed by endothelial cells across the respiratory and digestive tracts. As a serine protease, it is involved in the cleaving peptide bonds of proteins that have serine as the nucleophilic amino acid within the active site. The exact biological function of TMPRSS2 is largely unknown, although research has shown that it is involved in certain pathologies. TMPRSS2 is an endothelial cell surface protein that is involved in the viral entry and spread of corona viruses including severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) – the virus that causes COVID-19. Thus, ACE2 is responsible for viral entry in body & TMPRESS 2 is responsible for initiating pathogenesis of virus in lungs as well as spread of virus in other parts of body such as lungs, g.i.t etc. Blocking TMPRSS2 could potentially be an effective clinical therapy for COVID-19. Animal studies on TMPRSS2 blockers: Animal studies have shown that healthy wild-type mice infected with SARS-CoV develop acute pneumonia and exhibit body weight loss of up to 15%, though non die as a result and show recovery. TMPRSS2-/- knockout mice infected with SARS-CoV do not develop pneumonia or suffer any bodyweight loss with much lower viral replication in the lungs of these mice. Furthermore, wild-type mice have a strong expression of antigen- positive cells in the bronchiolar epithelial, but this expression was very weak in TMPRSS2-/- mice. Also, TMPRSS2-/- mice showed reduced inflammatory responses compared to wild-type mice. Thus, TMPRSS2 is needed for coronavirus viral replication in the lungs as. In conclusion, TMPRSS2 is an enzyme involved in the 'priming' of many viruses including coronaviruses such as SARS-CoV-2, allowing them to enter the body to cause disease (such as COVID-19). Interactions between the spike-domain on viruses and TMPRSS2 is critical for viral entry into epithelial cells in the respiratory (and digestive) tract. Inhibition of TMPRSS2 may serve to be an important therapy for COVID-19. Use of Mefenamic acid COVID-19 treatment: Mefenamic acid inhibits TMPRSS2 and there by inhibits virus entry and its replication studies show that a combination of ribavirin together with mefenamic acid was shown to be effective in reducing viral yield in cells infected with a positive- sense RNA. It was confirmed that Mefenamic acid, a primary compound in the NSAID group, has potential antiviral activity *in-vitro* and *in-vivo*, and this activity is better achieved when delivered in combination with the common antiviral drug, pathological signs were significantly reduced, which was ascribed to a combination of the antiviral and anti-inflammatory effects of mefenamic acid. It has been observed that there is a crucial role of NLRP3 inflammasome activation in the pathogenesis of diseases caused by SARS-CoVs, there is a role of inhibitors of the NLRP3 inflammasome in the context of inflammatory diseases and attention be drawn toward potential role of these (and similar agents) inhibitors in the treatment of SARS-CoV-2(COVID-19).[9,10]

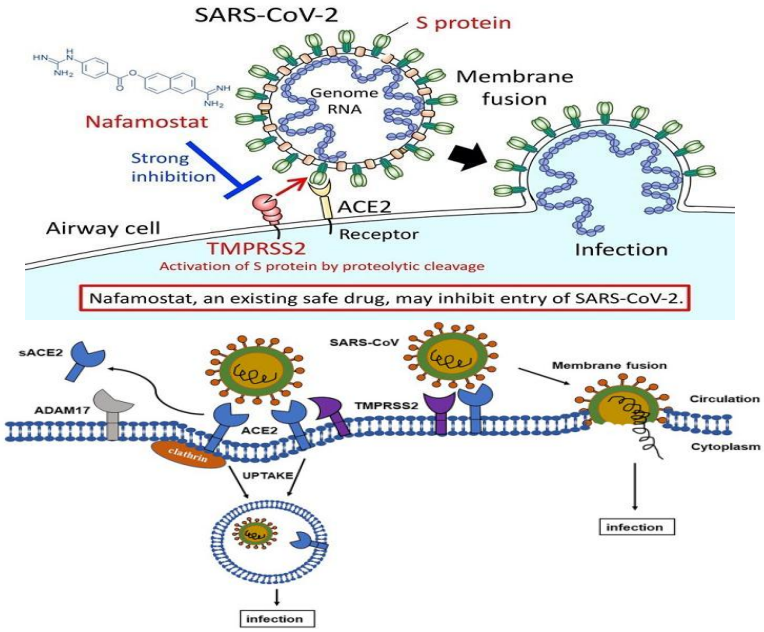


Figure-4: Nafamostat action on SARS-CoV-2.

Transmembrane protease, serine 2 is an enzyme that in humans is encoded by the TMPRSS2 gene.
Function: This gene encodes a protein that belongs to the serine protease family. The encoded protein contains a type II transmembrane domain, a receptor class A domain, a scavenger receptor cysteine-rich domain and a protease domain. Serine proteases are known to be involved in many physiological and pathological processes. This gene was demonstrated to be up-regulated by androgenic hormones in prostate cancer cells and down-regulated in androgen-independent prostate cancer tissue. The protease domain of this protein is thought to be cleaved and secreted into cell media after autocleavage. The biological function of this gene is unknown.[11,12]

ERG gene fusion: TMPRSS2 protein's function in prostate carcinogenesis relies on overexpression of ETS transcription factors, such as ERG and ETV1, through gene fusion. TMPRSS2-ERG fusion gene is the most frequent, present in 40% - 80% of prostate cancers in humans. ERG overexpression contributes to development of androgen-independence in prostate cancer through disruption of androgen receptor signalling. Relation to coronaviruses: Some coronaviruses, e.g. SARS-CoV-1, MERS-CoV, and SARS-CoV-2 are activated by TMPRSS2 and can thus be inhibited by TMPRSS2 inhibitors. "SARS-CoV-2 uses the SARS-CoV receptor ACE2 for entry and the serine protease TMPRSS2 for S protein priming. A TMPRSS2 inhibitor approved for clinical use blocked entry and might constitute a treatment option." One experimental candidate as a TMPRSS2 inhibitor for potential use against both influenza and coronavirus infections in general, including those prior to the advent of COVID-19, is the OTC (in most countries) mucolytic cough medicine bromhexine, which is also being investigated as a possible treatment for COVID-19 itself as well.[13,14]

Certain viruses, especially corona viruses require TMPRSS2 for their entry into the body. Recent studies have shown that corona require ACE2 (the main receptor) as well as TMPRSS2 for entry into epithelial cells. Both ACE2 and TMPRSS2 are expressed in nasal, bronchial, and gastrointestinal epithelium. TMPRSS2 activates; or primes, the spike protein domain (a key glycoprotein found on corona viruses) which leads to the virus fusing to the respiratory epithelia on the cell surface through binding to ACE2.[15,16]

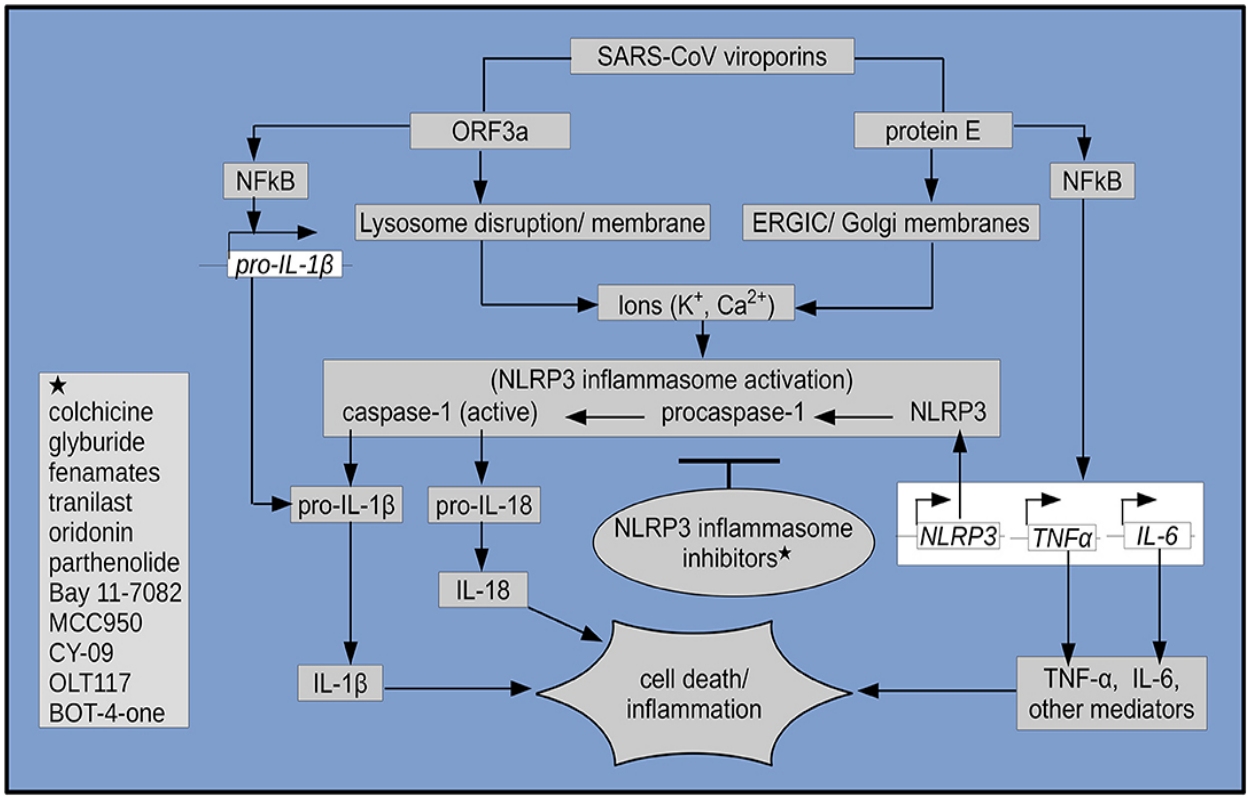


Figure-5: NLRP3 inflammasome activation.

CONCLUSION

These studies show that a combination of ribavirin together with mefenamic acid was shown to be effective in reducing viral yield in cells infected with a positive-sense RNA genome chikungunya virus. It was confirmed that Mefenamic acid, a primary compound in the NSAID group, has potential antiviral activity in vitro and in vivo, and this activity is better achieved when delivered in combination with the common antiviral drug, RIBA.8 Pathological signs were significantly reduced, which was

ascribed to a combination of the antiviral and anti-inflammatory effects of mefenamic acid. It has been observed that there is a crucial role of NLRP3 inflammasome activation in the pathogenesis of diseases caused by SARS-CoVs, there is a role of inhibitors of the NLRP3 inflammasome in the context of inflammatory diseases and attention be drawn toward potential role of these (and similar agents) inhibitors in the treatment of SARS-CoV-2 (COVID-19). Considering the clinical use of several NLRP3 inhibitor drugs for the treatment of other inflammatory diseases, further studies may determine potential usefulness of these agents in the treatment of COVID-19.9 The inhibition of protease inhibition has found to be an important part of treatment in the studies conducted using Camostat. The formation of M28 was found to be inhibited by mefenamic acid. It is thus possible for it to be a protease inhibitor Studies have reported the anti-viral activity of mefenamic acid and doxycycline. The inhibitory effect of mefenamic acid against RNA viruses has been estimated as 90% at a concentration of 30 μM.27 The synergistic antiviral effects of drug combinations are desirable, other pharmacodynamic consequences must be studied in detail before further clinical trials. Mefenamic acid can be used as an anti-antipyretic in patients of COVID19 with an additional benefit of it being also having the possibility of an anti-viral activity. Studies are required to validate this opinion so as to repurpose the use of Mefenamic acid in viral infections, such as of SARS-CoV-2.

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