MECHANISM BY WHICH IVERMECTIN COMBATS THE COVID-19 VIRUS

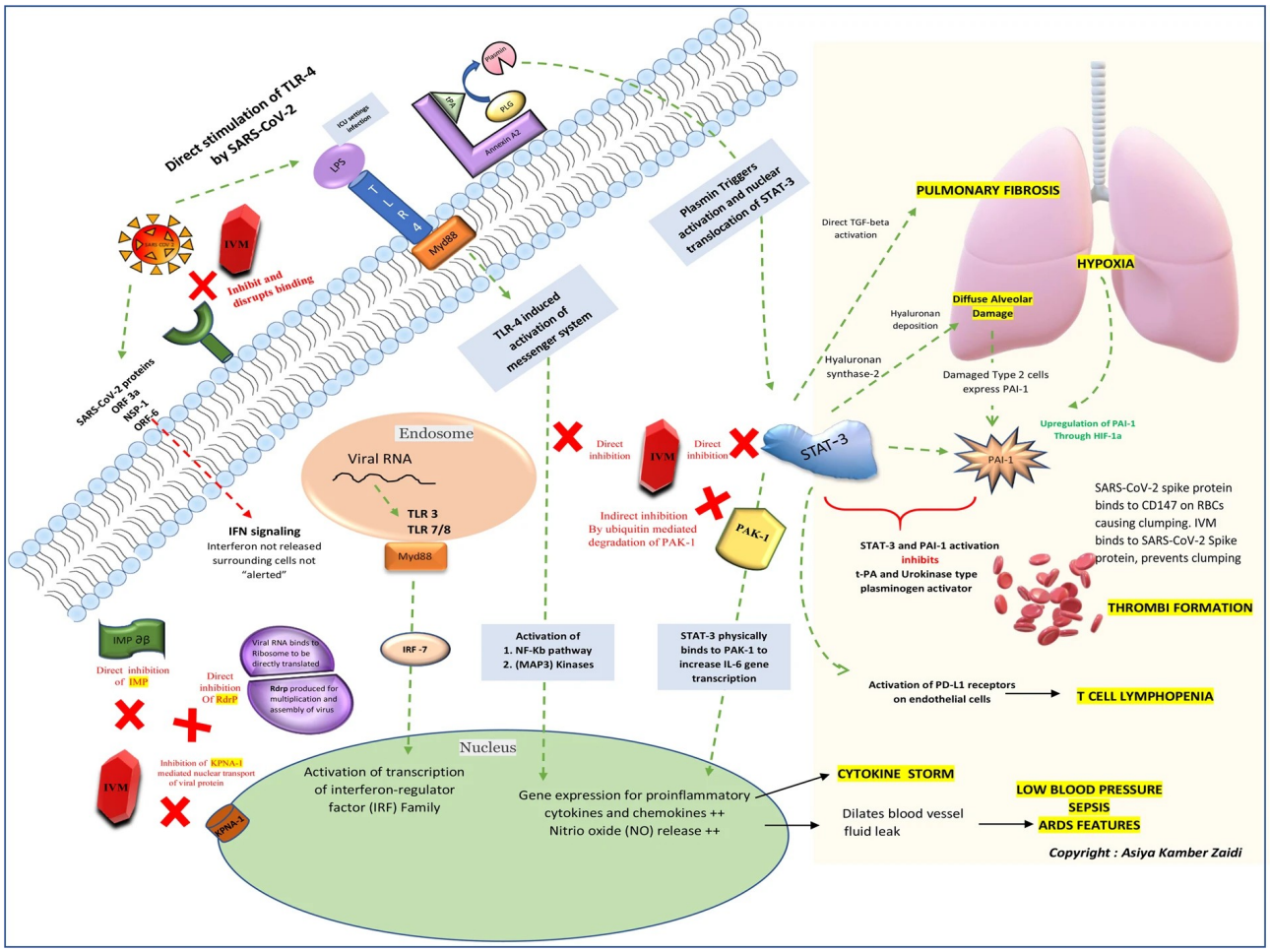

Figure 1: Depiction of the multifaceted action of IVM against RNA viral activity

Source Reference: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8203399/
"The mechanisms of action of Ivermectin against SARS-CoV-2: An evidence-based clinical review article"

General

Ivermectin interferes with RNA viruses, and with COVID-19 in particular, through a number of different mechanisms besides that of being a Lysosomotropic Ionophore which will transfer the Zinc Cation (Zn+) into the cytoplasm of human cells where it effectively interferes with viral replication. Zinc, itself, plays a multifaceted role in the function of the human immune system. (See: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6628855/figure/fig1/)

Ivermectin(**IVM**) (shown as a red block in Fig 1) inhibits and disrupts binding of the SARS-CoV-2 S protein at the angiotensin-converting-enzyme type 2 (**ACE-2**) receptors (shown as a green dish on a stem). The green dotted lines depict activation pathways and the red dotted lines depict the inhibition pathways.

The Toll-Like Receptor 4 (**TLR-4**) receptors are directly activated by SARS-CoV-2 and also by Lipopolysaccharide (**LPS**) mediated activation, seen during Intensive Care Unit (**ICU**) settings, causing activation of Nuclear Factor Kappa-light-chain-enhancer of activated B cells (**NF-Kb**) pathway and Mitogen-Activated Protein (**MAP**)3 Kinases leading to increased intranuclear gene expression for proinflammatory cytokines and chemokines (responsible for cytokine storm) and

Nitrous Oxide(**NO**) release (responsible for blood vessel dilatation, fluid leak, low blood pressure, Acute Respiratory Distress Syndrome (**ARDS**) and sepsis).
The NF-Kb and Signal Transducer and Activator of Transcription(**STAT**)-3 pathway activation is central to the pathogenesis and sequelae of COVID-19. STAT-3 physically binds to P21 Activated Kinase 1 (**PAK-1**) and increases Interleukin 6 (**IL-6**) transcription. The Annexin A2 at the cell surface converts plasminogen (**PLG**) to plasmin under the presence of tissue-like plasminogen activator (**t-PA**). Plasmin triggers activation and nuclear translocation of STAT-3. An upregulation of STAT-3 stimulates hyaluronan synthase-2 in the lung cells causing hyaluronan deposition leading to diffuse alveolar damage and hypoxia. STAT-3 also directly activates Transforming Growth Factor beta (**TGF-beta**) initiating pulmonary fibrosis; a typical characteristic of SARS-COV-2 lung pathology. The damaged type 2 cells express Plasminogen Activator Inhibitor-1 (**PAI-1**) and an already hypoxic state also causes an upregulation of PAI (through Hypoxic inducible factor-1) along with direct stimulation by STAT-3. Simultaneous STAT-3 and PAI-1 activation inhibits tissue-like Plasminogen Activator (**t-PA)** and urokinase-type plasminogen activator leading to thrombi formation. Also, the SARS-CoV-2 spike protein binds to the Cluster of Differentiation 147 (CD147) protein on red blood cells and causes clumping. *IVM in turn, binds to SARS-CoV-2 Spike protein and hence prevents clumping*. T cell lymphopenia in COVID-19 can also be attributed to the direct activation of Programmed Death-Ligand 1(**PDL1)** receptors on endothelial cells by STAT-3..

*IVM directly inhibits the Nuclear Factor kappa-light-chain-enhancer of activated B cells (**NF-kb**) pathway, STAT-3, and indirectly inhibits PAK-1 by increasing its ubiquitin-mediated degradation*.
The natural antiviral response of a cell is through interferon regulatory genes and viral RNA mediated activation of TLR-3 and TLR7/8- Myd88 activation of transcription of Interferon-Regulator (**IRF**) family. For a virus to establish an infection, this antiviral response needs to be inhibited by blocking interferon production. The proteins such as importin and KaryoPherin Subunit Alpha 1 (**KPNA-1**) mediate nuclear transport of viral protein and subsequent Interferon (**IFN**) signaling. The SARS-CoV-2 proteins (ORF-3a, NSP-1, and ORF-6) directly block IFN signaling causing the surrounding cells to become unsuspecting victims of the infection. *IVM inhibits both importin a-b (green) as well as the KPNA-1 receptors (brown) causing natural antiviral IFN release. IVM also inhibits viral RNA dependent RNA polymerase (**RdRp**), responsible for viral replication*.

Index of Terms:
IVM Ivermectin.
ACE-2 angiotensin-converting-enzyme type 2.
Annexin A2 also known as annexin II is a protein that in humans is encoded by the ANXA2 gene. Annexin 2 is involved in diverse cellular processes such as cell motility, linkage of membrane-associated protein complexes to the actin cytoskeleton, endocytosis, fibrinolysis, ion channel formation, and cell matrix interactions.
CD147. Cluster of Differentiation 147 (CD147) is a protein that in humans is encoded by the Basigin (BSG) gene. BSG also known as “Extracellular Matrix Metalloproteinase Inducer” (EMMPRIN).
LPS Lipopolysaccharide,
TLR Toll-like receptor,
t-PA tissue-like Plasminogen Activator,
PDL1 Programmed Death-Ligand 1 also known as cluster of differentiation 274 or B7 homolog 1 is a protein that in humans is encoded by the CD274 gene.
PLG Plasminogen.
PAI-1. Plasminogen Activator Inhibitor-1 also known as endothelial plasminogen activator inhibitor is a protein that in humans is encoded by the SERPINE1 gene. Elevated PAI-1 is a risk factor for thrombosis and atherosclerosis.
IMPab Importin alpha-beta,

IL6 Interleukin 6 is an interleukin (mammalian protein) that acts as both a pro-inflammatory cytokine and an anti-inflammatory myokine. In humans, it is encoded by the IL6 gene. In addition, osteoblasts secrete IL-6 to stimulate osteoclast formation. Smooth muscle cells in the tunica media of many blood vessels also produce IL-6 as a pro-inflammatory cytokine.
RdRp RNA dependant RNA polymerase,
TGF-beta or TGFB Transforming Growth Factor beta is a multifunctional cytokine belonging to the transforming growth factor superfamily that includes three different mammalian isoforms and many other signaling proteins. TGFB proteins are produced by all white blood cell lineages.
TLR-4 Toll-like receptor 4, a protein-coding gene in the species Homo sapiens. The Toll-like receptor 4, also designated as CD284, is a key activator of the innate immune response and plays a central role in the fight against bacterial infections. TLR4 is a trans-membrane protein of approximately 95 kDa (95 kiloDaltons = 95grams/mole) that is encoded by the TLR4 gene.
IFN Interferon. Interferons are a group of signalling proteins made and released by host cells in response to the presence of several viruses. In a typical scenario, a virus-infected cell will release interferons causing nearby cells to heighten their anti-viral defences.
KPNA-1 Karyopherin Subunit Alpha 1,
NF-kB Nuclear Factor kappa-light-chain-enhancer of activated B cells,
MAP3 Mitogen-Activated Protein Kinases. Efficient regulation of type I interferon and NF-κB signalling by members of the mitogen-activated protein (MAP) kinase kinase kinase (MAP3K) family plays an important role in antiviral immunity.
PAK-1 P21 Activated Kinase 1,
RdRp RNA-dependent RNA polymerase or RNA replicase is an enzyme that catalyzes the replication of RNA from an RNA template. Specifically, it catalyzes synthesis of the RNA strand complementary to a given RNA template.
STAT-3 Signal transducer and activator of transcription 3,
PAI-1 Plasminogen activator inhibitor-1,
HIF-1 Hypoxia-Inducible Factor