Ingenew Pharma
Montreal, Quebec, Canada

The Hesperidin Study in COVID-19 Patients

Scientific Rational Supporting the Clinical Program:
The Early Phase (January-May 2020)

Prevent Entry and Replication of SARS-CoV-2
by Inhibiting both Spike(S) Protein and 3CLpro
AND
Assist the Primary Immune Response by
Reducing Inflammatory Mediators, Cytokine Storm and
The Potential of Neuronal and Cardiopulmonary Injuries

Extensive Review of Recent and Historical Scientific and Medical Literature
Focused on SARS-CoV/SARS-CoV-2/COVID-19

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I. Executive summary of The Hesperidin Study in COVID-19 patients

Treatment of COVID-19 patients with hesperidin for 14 days to:
- ↓ Reduce the severity of illness and requirement for hospitalization in COVID-19
- ↓ SARS-CoV-2 by inhibiting its viral dynamics (replication)
  - Prevent entry/replication by targeting **both** Spike(S) protein **and** 3CLpro
- Assist the primary immune response during the 7 days lag time period
  - ↓ Pro-inflammatory mediators of cytokine storm
  - ↓ Potential myocarditis, heart failure and/or coronary artery diseases
  - ↓ Potential neurological injuries
  - ↓ Potential lower respiratory tract injuries
- ↓ Burden on the healthcare system by ↓ number people seeking medical assistance

II. SARS-CoV-2; Its structure and infection process originating from the 4 initial points of infection

During the second week of December 2019, a series of pneumonia cases of unknown origin emerged from the Huanan Seafood Market in Wuhan, Hubei, China with clinical presentations greatly resembling viral pneumonia (Figure 1)[1-3]. The Wuhan local health authority issued an epidemiological alert on Dec 31, 2019 and closed the Huanan seafood market within 48 hours. RNA sequencing analysis from lower respiratory tract samples of patients indicated a novel β-coronavirus[4,5], which was initially referred to as novel coronavirus pneumonia (2019-nCoV) later renamed SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2)[6,7].

On April 30th, 2020, approximately 6 months after the first reported cases in China, more than 3,4 million people, had been infected worldwide and the closed cases reported a death rate of 19% with the R_0 estimated between 2.24 and 3.58[7,8]. In less than 60 days, more than 1 million people in the United States, 50,000 in Canada and over 25,000 in Quebec had been infected by SARS-CoV-2. By September 30th, 2020, the infection had spread to over 34 million people with more than 1 million people dying from COVID-19 worldwide. While the World Health Organization (WHO) declared SARS-CoV-2 (COVID-19) outbreak a global pandemic on March 11, 2020 it has already inflicted personal, medical, and sociological repercussions on a global scale.

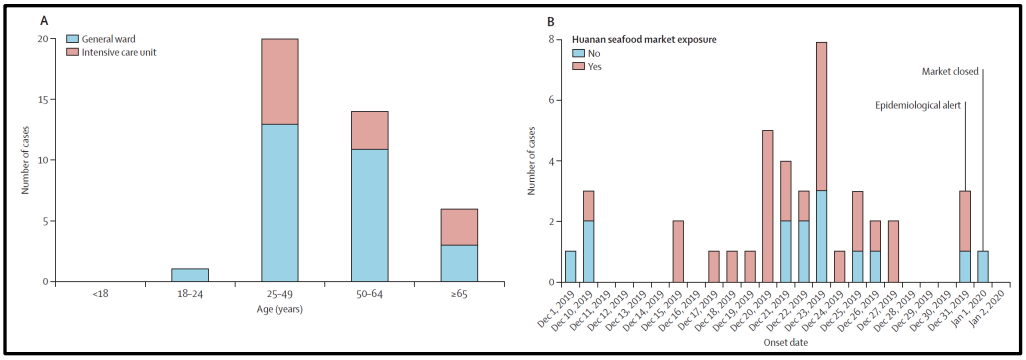

Figure 1: Date of illness onset and age distribution of patients with laboratory-confirmed 2019-nCoV infection. (A) Number of hospital admissions by age group and (B) Distribution of symptom onset date for laboratory-confirmed cases

SARS-CoV-2 is the 3rd β-coronavirus in the last 20 years to cause an epidemic as SARS-CoV (2002) and Middle East Respiratory Syndrome coronavirus (MERS-CoV) have led to more than 10,000 cumulative cases with mortality rates of 10% and 37% respectively[9,10].

Coronaviruses are enveloped non-segmented positive-sense RNA viruses belonging to the family Coronaviridae (order Nidovirales) and broadly distributed in humans and other mammals[11]. The single RNA strand of SARS-CoV-2 and SARS-CoV encode for highly conserved proteins such as Spike(S) protein and proteinases essential to their replication like 3C-Like proteinase (3CLpro) also cited in the literature as Main proteinase (Mpro)(Figure 2)[12-14].

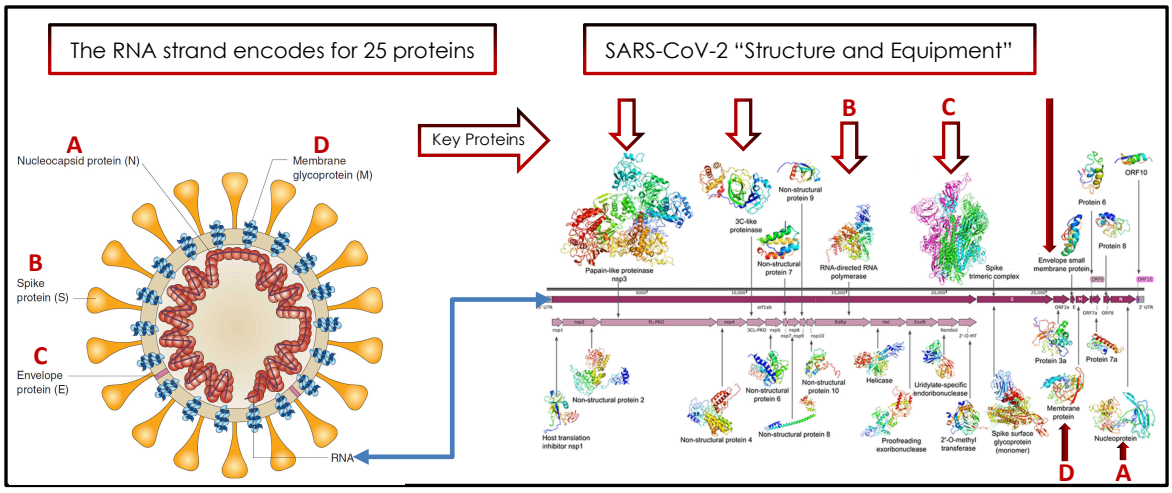

Figure 2: The 26 structural components of SARS-CoV-2

SARS-CoV-2 capsule is composed of membrane (M), envelope(E) and Spike(S) proteins. The infection process is initiated when the region binding domain (RBD) of both Spike(S) protein and the angiotensin-converting enzyme 2 receptors (ACE2) on the cell surfaces of the host bind together (Figure 3)[15-17].

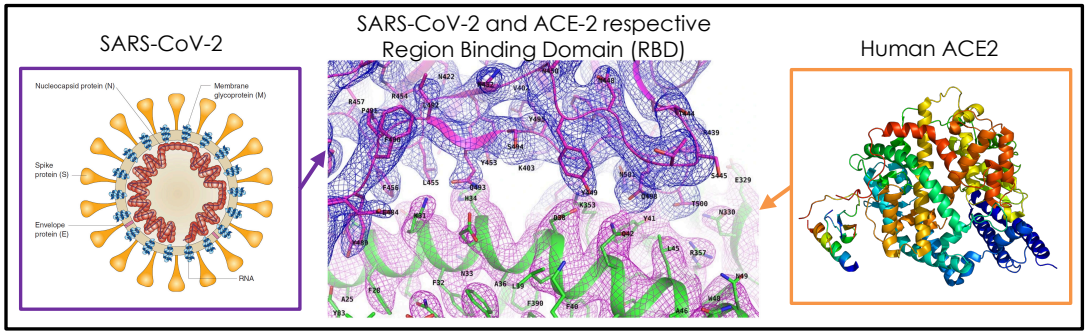

Figure 3: The "first contact" between SARS-COV-2 Spike(S) protein and human ACE2 respective region binding domain (RBD).

This biding between both RBD triggers the TMPRSS2 (Transmembrane protease serine type 2), a cell surface serine protease that, under normal conditions regulates cell-cell and cell-matrix interactions, to cleave Spike(S) protein into 2 subunits: the N-terminal surface unit that includes the RBD namely S1 and the C-terminal transmembrane unit who's role is to initiate the membrane fusions process between the host cell and SARS-CoV-2 (Figure 4)[18]. Metallopeptidase domain 17 (ADAM17) that belongs to the protein family of disintegrins and metalloproteases was also reported to cleave the S1 and S2-S2'. Moreover, TMPRSS2 was found to compete with ADAM17 but only cleavage by TMPRSS2 resulted in augmented SARS-CoV Spike(S) proteins-driven entry[19].

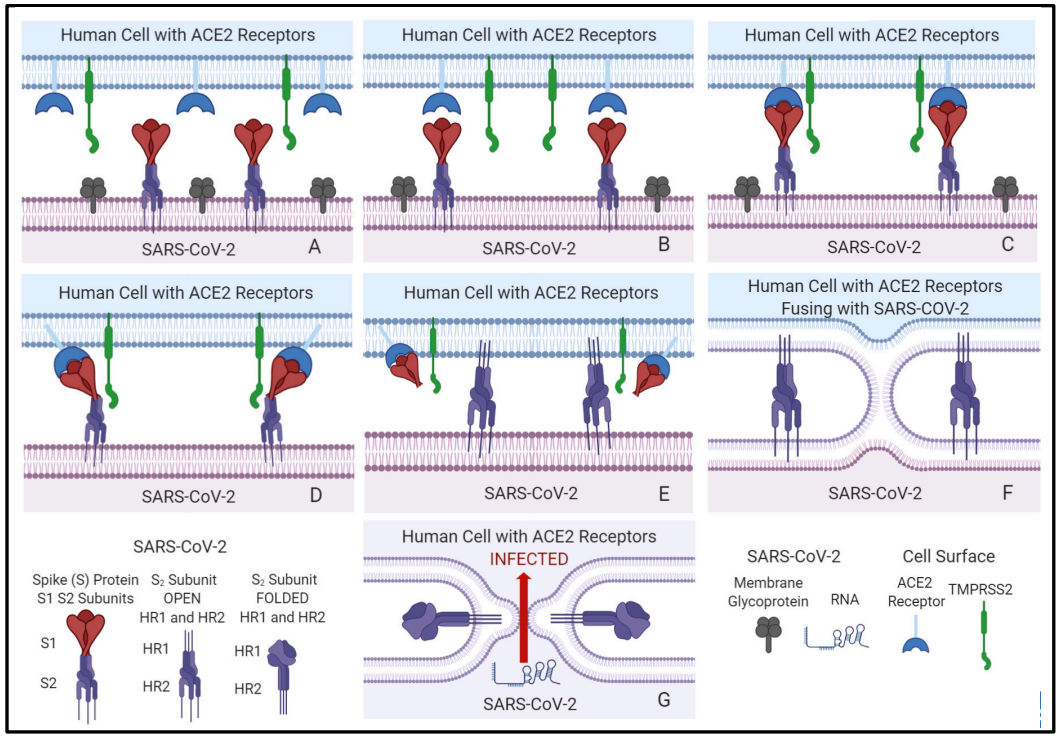

Figure 4: SARS-CoV-2 infection process: A) SARS-CoV-2 searches the environment with Spike(S) proteins looking for ACE2 receptors. B) RBD of both Spike (S) protein of SARS-COV-2 and the Cell's ACE2 develop the affinity binding process. C) Binding of Spike(S) with ACE2 trigger the serine proteases TMPRSS2. D)TMPRSS2 cleave the Spike(S) at 2 locations: S1-S2 and S2-S2' releasing the S1 subunit and exposing the HR1-HR2 of the C-terminal domain of Spike(S) protein. E) HR1 imbed itself into the phospholipid bilayer of the cell (Open HR1-HR2). F) Once

embedded HR1-HR2 initiate the bilayer fusion between SARS-COV-2 and host cell by folding onto themselves (Folded HR1-HR2). G) By creating an entry port, the fusion marks the end of the infection stage by SARS-COV-2 and the beginning of the viral replication by allowing the genetic material such as RNA and necessary viral proteins to initiate viral replication (Created with Biorender.com).

The predominant location of the initial viral infection by SARS-CoV-2 plays a significant role in the infection/immunization days of onset and potential severity. Human physiology presents 4 initial points of infections to SARS-CoV-2: tracheal, alveolar, nasal and ocular. While these 4 points of infections all contains cells that exhibit ACE2 receptors on their surface they can lead to different symptoms, days of onset and infection pattern by SARS-CoV-2 (Figure 5).

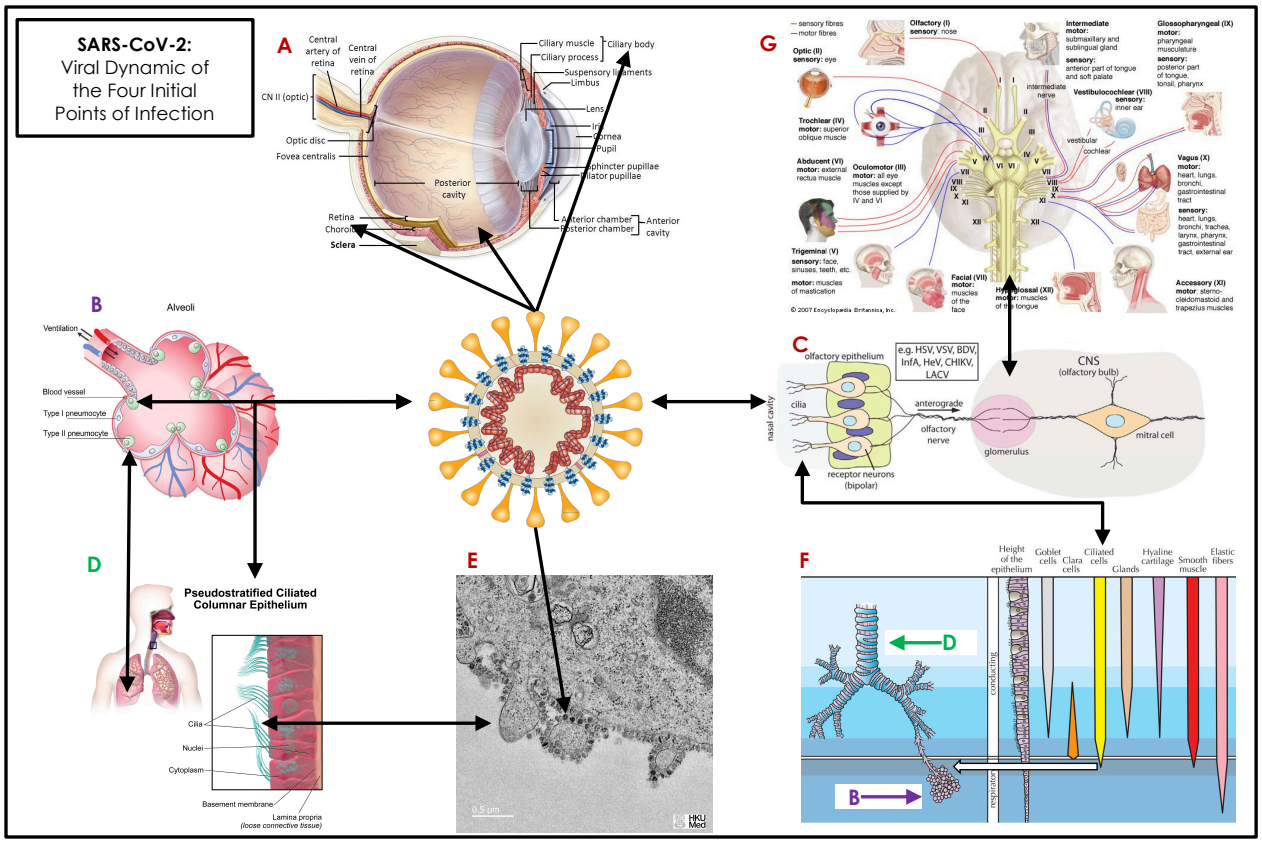

Figure 5: The 4 initial points of infections by SARS-CoV-2 are guided by the presence of ACE2 on cells exposed to the environment. A) Ocular path: ACE2 from the retina, aqueous humor and cilia. B) Lower respiratory tract path: ACE2 on pneumocyte type II cells of alveoli. C) Upper respiratory tract path: ACE2 on the cilia of olfactory bulb receptor neurons. D) Lower respiratory tract path: ACE2 on the cilia of the bronchotracheal tree. E) First electron microscopy picture of SARS-CoV-2 (dark dot) surrounding a cilia from the bronchotracheal tree. F) Representation of the location of ACE2 containing ciliated cells along the bronchotracheal tree. G) Central nervous system (CNS) and sympathetic/para-sympathetic nervous systems conduit for extended neurotropic paths.

Infection by SARS-CoV-2 is a combination of viral kinetics and dynamics. If the infection is predominantly initiated orally (Figure 5D)[20], normal breathing patterns will allow for SARS-CoV-2 to be transported predominantly to the lower respiratory tract and parenchyma. Viral kinetics is initiated when Spike(S) protein from SARS-CoV2 binds to the ACE-2 present on their cell surface of the respiratory epithelium cilia in the lower respiratory tract (Figure 5E)[21]. As cilia are present throughout the tracheobronchial tree (figure 5F)[22], it enhances the infection surface and corresponding viral dynamics; the production of virions/mm^2 of surface as opposed to an ACE2 scarce area[23].

As SARS-COV-2 descend along the lower respiratory tract they can/will reach the parenchyma; the portion of the lungs responsible for the oxygen/carbon dioxide (O_2/CO_2) exchange (Figure 5B)[24]. Within the parenchyma, pneumocyte type II cells of alveoli also exhibit ACE-2 on their cell surface. It has been reported that SARS-CoV (2002) and most likely SARS-CoV-2 are able to invade with a high degree of specificity the type II cells when compared to the type I or macrophages[25]. Infection of the type II and ensuing for virion production depletes the alveoli of the very cells responsible for pulmonary surfactant production, essential for efficient exchange of gases and maintaining the structural integrity of alveoli. Atelectasis (partial/complete collapse of alveoli) is referred to as either acquired for fully formed alveoli or neonatal for underdeveloped alveoli in very-low-birth-weight (VLBW) pre-term neonates.

Acquired Atelectasis has been reported in more severe cases of COVID-19 patients especially those defined as suffering from acute respiratory distress syndrome (ARDS) and requiring mechanical ventilation[26-28]. VLBW preterm neonates born before the 32nd week of gestation afflicted with neonatal atelectasis were historically reported as suffering from hyaline membrane disease and more recently defined as neonatal respiratory distress syndrome (NRDS). The pre-term (<32nd week) have immature type II cells, hence insufficiently developed to produce surfactant. Today, the pre-term can be prescribed commercial surfactant and/or continuous positive airway pressure (CPAP) assistance a form of assisted ventilation[29,30].

Sticking similarities between critically ill SARS-CoV (2002)/COVID-19 patients requiring ventilator assistance and VLBW pre-term neonates go beyond treatment approaches as they are also found in clinicopathology investigations of lungs during autopsy of both types of patients. Histopathological examination of SARS (2002)[31] and COVID-19[32] patients reported similar findings. Namely, fibrinous and hemorrhagic inflammation in most pulmonary alveoli. The alveoli were thickened with interstitial mononuclear inflammatory infiltrates, diffuse alveolar damage (DAD), capillary engorgement, hyaline membrane formation and capillary microthrombosis. Furthermore, comparative pathogenesis studies from 2 groups reported that pneumocyte type II cells of SARS-CoV (2002) fatally infected patients had been heavily infected/destroyed and neither cytokeratin nor surfactant could be quantitated. Similar observations were reported in a SARS-CoV(2002) animal model[33]. As a consequence of the severity/fatality of the infection, they reported that a "signal" was sent to the undifferentiated embryonic stem cells via the stem/progenitor OCT-4 and CD34 to generate new type II cells when compared to type II cells harvested from healthy donor and subsequently infected with SARS-CoV(2002)[34,35]. Unfortunately, the viral dynamics of such a signal induction delivers to the alveoli the infecting target for SARS-CoV (2002) enhancing the grounds of a highly infectious cycle. The type II cells from healthy donors also revealed that, even for a small

donor pool, expression of ACE2 was quite variable among different individuals leading to differed susceptibility to SARS-CoV(2002) infection[35].

Predominant initial infection by SARS-CoV-2 of the upper respiratory track (nasal) facilitates viral infection of the cilia from receptor neurons (bipolar) intercalated in the olfactory epithelium within nasal cavity who also possess ACE2 on their cell surface and most likely can account for the reported "lost sense of smell" (Figure 5C)[36-38]. Under a normal respiratory pattern, infection of the lower respiratory tract should also be expected (Figure 5F). However, infection of the neuronal olfactory epithelium allows an entry point to the central nervous system for SARS-CoV-2. Seminal pre-clinical studies related to the neurotropic impact were conducted with HCoV(OC43); a β-coronavirus presenting SARS-CoV(2002) serological cross-reactivity and one of seven known coronaviruses to infect humans[39]. After intranasal inoculation of the mouse model, HCoV-OC43 neuroinvasive path followed a selected infection of the olfactory bulb at day 3 post infection (dpi) with no infection detected in the cortex or other brain structures, illustrating transneuronal spreading of the virus. However by the 7 dpi, the virus has disseminated to the entire CNS, as reported by the presence of immunopositive cells throughout the brain[40]. By day 13 dpi, the virus had spread from the CNS to peripheric organs, such as heart, lungs, spleen, and to a lesser extent liver and muscles as opposed an intraoral inoculation, from which the presence of virus or virus gene products could not be detected in any tissue tested[41,42]. Neurotransmission via the olfactory bulb is not unique to the SARS-CoV family as other viruses such as H5N1, HIV, HSV, HCMV and CHIKV have also been reported to utilize the same infection path[43,44].

While ocular infection by SARS-CoV-2 is most likely not the predominant route of infection[45,46] by SARS-CoV-2 (Figure 5A)[47] but it was the most devastating one for the ICU medical team attending the first patients during the Wuhan outbreak. Of the first 4 deaths related to physician/nurses of ICU units in Wuhan[48], 3 were Ophthalmologists and the fourth one, Dr. Guangfa Wang, a pneumonia expert, indicated having been infected via his unprotected eyes during a tour of the critical care wards in Wuhan. Neurotropic mechanisms have suggested an initial ocular infection by SARS-CoV-2 via the aqueous humor, cilia or retina as they all have ACE2 receptors[49,50]. Ocular cilia and retina infection paths also allow SARS-CoV-2 neurotransmission via the cilia and optic nerves leading to neuro-infection of the CNS. The ensuing neuro-virulence and sequalae are mirrored to the upper respiratory tract infection[51].

Neurotransmission, whether ocular or nasal, lead inevitably to neuro-virulence within the central nervous system (CNS) of COVID-19 patients (Figure 5G)[52]. Neurotropic impact could be expected with multi-organ neurotransmission of SARS-CoV-2 culminating in systemic infection. Direct infection of the respiratory tract can also lead to devastating effect such as atelectasis and the need in, critical cases, to mechanical ventilator assistance. While the scientific literature provides multi-virus neurotropic paths to systemic infection, similar evidence for the bronchotracheal path are scarce. Most importantly, severity of COVID-19 clinical manifestations could be anticipated to be a combination of key factors such as initial point of entry, initial SARS-CoV-2 load along with the patient' medical history and intrinsic immune response.

III. Repercussions of SARS-CoV-2 in COVID-19 patients

The majority of COVID 19 patients will have clinical symptoms that are defined as asymptomatic or mildly symptomatic hence not requiring hospitalization. However, early clinical studies of COVID-19 patients that were hospitalized in Wuhan have shown that, at onset, patients frequently show symptoms associated with viral pneumonia, most commonly fever, cough, sore throat, myalgia, and fatigue[53]. When patients were admitted to the hospital in Wuhan (the same algorithm is now implemented globally), they underwent \a stratification process whereby their medical condition were defined[54] as severe (defined as tachypnoea [≥30 breaths per min], oxygen saturation ≤93% at rest, or PaO2/FiO2 ratio <300 mm Hg) or critical[55] (respiratory failure requiring mechanical ventilation, septic shock, or other organ dysfunction or failure that requires intensive care) (Figure 6)[56].

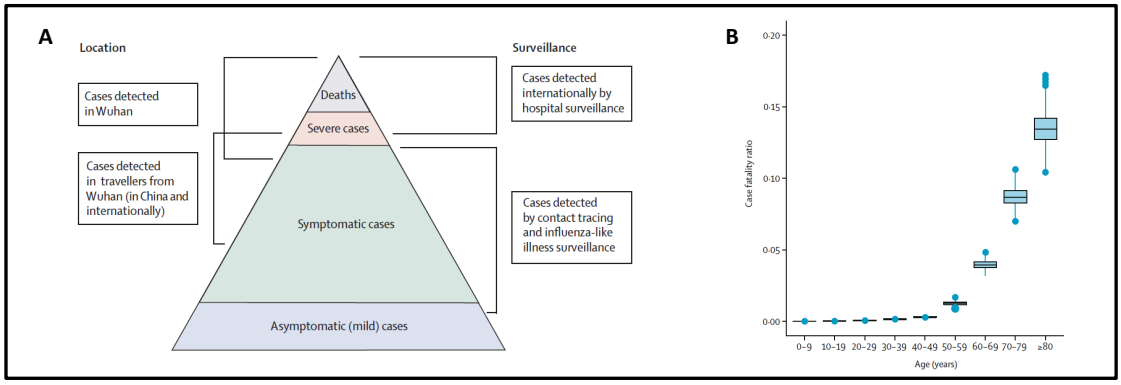

Figure 6: (A) Spectrum of COVID-19 disease in which patients meeting the criteria for severe or critical cases are likely to be identified in hospital settings. (B) Estimates of the case fatality ratio by age group during the initial Wuhan outbreak (Dec 2019).

Once SARS-COV-2 has initiated the infection of a, now defined COVID-19 patient, the immunization process of the host begins as the virus presents neoantigens[57]. Hence after neoantigen exposure, B and T lymphocytes differentiates into effector immunoglobulin G (IgG) (antibody) producing and effector cytotoxic/helper/memory cells, respectively. For both B and T cells in a typical immune response to a neoantigen exposure, the latency between the infection and development of the primary response (logarithmic phase) is characterized by a lag phase. The lag phase is the initial activation of B and T cells upon encounter with the neoantigen and classically thought to be 4 to 7 days, but it varies depending on route of exposure and the antigen itself. For many neoantigens the latency (lag phase) between the initial infection and development of the primary IgG response is 7 to 10 days[58].

During infection period of 4-10 days the immune system of the host is incapable of fighting/defending against neoantigens like SARS-CoV-2 as the generation of IgG capable of neutralizing SARS-COV-2 are created for the first time during those 4 to 10 days (Figure 7)[59].

In view of the immunological vulnerability of COVID 19 patients during the lag time phase of immunization, viral dynamics of SARS-COV-2, including viral shedding, in mild and severe cases become the key focal point of any drug treatment attempting to inhibit entry and/or replication of SARS-CoV-2. Viral shedding refers to the expulsion and release

of SARS-CoV-2 progeny (virions) following successful reproduction within infected cells bearing ACE2 receptors in a COVID-19 patient[60]. Viral load of SARS-CoV-2 peaks within the first week of disease onset but the algorithm of infection is complex as the spectrum of infection/immunization can be very heterogeneous. A clinical trial studied the viral RNA shedding patterns observed in patients with mild and severe COVID-19 in which no patient died from the infection. The mean viral load (Ct) of severe cases was around 60 times higher than that of mild cases, suggesting that higher viral loads might be associated with severe clinical outcomes.

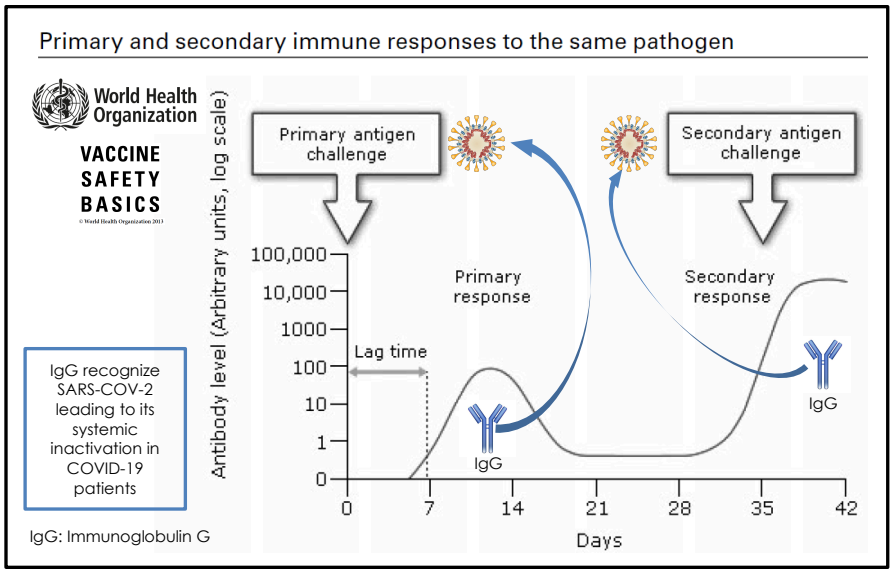

Figure 7: The lag time phase, the primary and second antigen (SARS-CoV-2) challenges

Furthermore, the viral loads were stratified according to the day of disease onset at the time of sampling (ΔDCt method= ($Ct_{sample} - Ct_{ref}$)) and they reported that the ΔCt values of severe cases remained significantly lower for the first 12 days after onset than those of corresponding mild cases. Mild cases were found to have an early viral clearance, with 90% of these patients repeatedly testing negative on RT-PCR by day 10 post-onset. By contrast, all severe cases still tested positive at or beyond day 10 post-onset (Figure 8)[61]. Hence, patients with severe COVID-19 had high viral loads and long virus shedding period suggesting a causality between COVID-19 severity/prognosis and viral shedding profile.

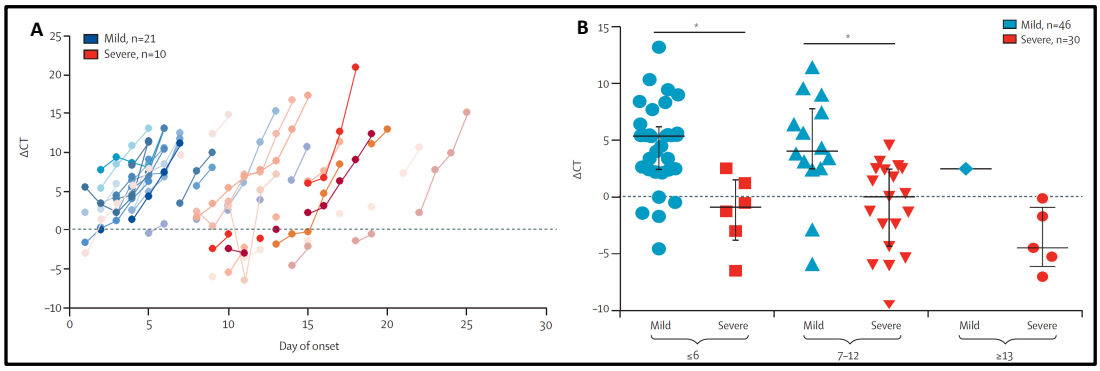

Figure 8: SARS-CoV-2 dynamics in patients with mild and severe COVID-19. (A) ΔCT values of serial samples from patients with mild and severe (*p<0·005) and (B) ΔCT values from patients with mild and severe at different stages of disease onset.

COVID-19 patients were stratified during diagnosis as critical, severe, mild, or asymptomatic in the early onset of the pandemic. The amplitude of COVID-19 clinical symptoms such as severity were further characterized with cytokine and chemokine measurement related to the intensity of cytokine storm occurring within each COVID-19 patient[62-64].

Cytokines and chemokines were studied in clinical trials focusing on severe (non-Intensive Care Unit-(ICU)) critically ill (ICU) COVID-19 patients. During one of those trials, the effects of SARS-CoV-2 on the production of cytokines, chemokines, interferon and/or growth factors such as: IL1β, IL1Ra, IL2, IL4, IL5, IL6, IL7, IL8 (CXCL8), IL9, IL10, IL12p70, IL13, IL15, IL17a, CCL11, basic FGF2, GCSF (CSF3), GMCSF (CSF2), IFNγ, IP10 (CXCL10), CCL2 (MCP-1), CCL3 (MIP1A), CCL4 (MIP1B), PDGFB, CCL5 (RANTES), TNFa, and VEGFa were measured in the acute phase of the illness with a median time of 4 days from being transferred to a designated hospital to the blood sample collection[1,65].

Initial plasma levels (concentrations) in COVID-19 patients of IL1β, IL1Ra, IL7, IL8, IL9, IL10, basic FGF, GCSF, GMCSF, IFNγ, IP10, CCL2, MIP1A, MIP1B, PDGF, TNFa, and VEGF concentrations were higher in both ICU patients and non-ICU patients than in healthy controls. Furthermore, comparison between ICU and non-ICU patients showed that plasma concentrations of IL2, IL7, IL10, GCSF, IP10, CCL2, MIP1A, and TNFa were higher in ICU patients than non-ICU patients[66].

Non-ICU patients infected with SARS-CoV-2 had high amounts of IL1β, IFNγ, CCL2 and IP10 while patients requiring ICU admission had additionally higher concentrations of GCSF, IP10, MCP1, MIP1A, and TNFa suggesting that the cytokine storm was associated with disease severity (Figure 9)[1].

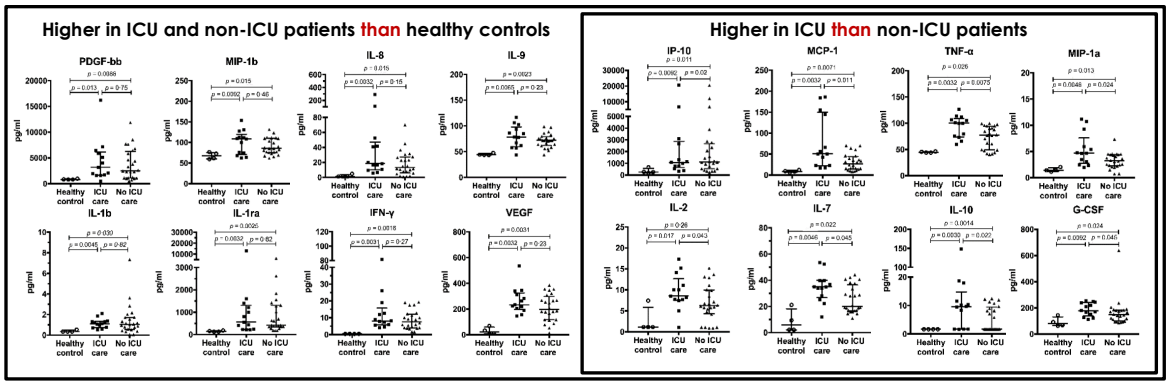

Figure 9: Plasma level of cytokines and chemokines from COVID-19 ICU (n=13) and non-ICU (n=28) patients and healthy controls (n=4).

The sequalae of SARS-COV-2' ophthalmic and olfactive neuroinvasion routes leading to the central nervous system (CNS) have been reported[36,67] including the first case meningitis/encephalitis in a COVID-19 patient[68]. The patient had fatigue and fever on the first day, saw a physician on day 2 and 5 but was found unconsciousness and lying on the floor in his vomit 4 days later. During transport to the hospital (Day 9), he had transient generalized seizures that lasted about a minute and obvious neck stiffness. The specific SARS-CoV-2 RNA was not detected in the nasopharyngeal swab but was detected in a Cerebro-Spinal Fluid (CSF) sample. At day 15, the patient continued treatment in ICU for bacterial pneumonia and impaired consciousness due to encephalitis. Presence of SARS-CoV (2002) was also reported in the CSF of a patient who exhibited similar neurological

manifestations of infection[69]. Furthermore, it was reported that SARS-CoV (2002) genome sequences were detected in the brain of all 18 autopsies performed[70] of fatally infected patients.

A retrospective case series study was performed on the neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China over the course of 1 month starting January 16, 2020. 214 hospitalized patients with laboratory confirmed diagnosis of SARS-CoV-2 infection had their neurological symptoms evaluated by 2 trained neurologists and classified as: CNS symptoms or diseases (headache, dizziness, impaired consciousness, ataxia, acute cerebrovascular disease, and epilepsy), peripheral nervous system (PNS) symptoms (hypogeusia, hyposmia, hypopsia, and neuralgia), and skeletal muscular symptoms. Of 214 patients studied, 88 were severe and 126 were non-severe patients. 78 [36.4%] patients had neurologic manifestations. More severe patients were likely to have neurologic symptoms (40 [45.5%] vs 38 [30.2%]), such as acute cerebrovascular diseases (5 [5.7%] vs 1 [0.8%]), impaired consciousness (13 [14.8%] vs 3 [2.4%]) and skeletal muscle injury (17 [19.3%] vs 6 [4.8%]). Severe patients were older (58.7 ± 15.0 years vs 48.9 ± 14.7 years), had more underlying disorders (42 [47.7%] vs 41[32.5%]), especially hypertension (32 [36.4%] vs 19 [15.1%])[71].

Due to the neurotropic potency of SARS-COV-2, dysregulation of renin-angiotensin-system (RAS) as an important contributor to the pathophysiology of COVID-19[72]. Neurotransmission enables SARS-COV-2 to target the RAS of the central nervous system (CNS). RAS is a key regulator of cardiovascular and renal homeostasis, but also plays important roles in mediating physiological functions in the CNS. As a major contributor to RAS, ACE2 is typically counterbalancing the deleterious effects exerted by Ang II[73].

ACE2 primary physiological role in RAS is the enzymatic conversion of angiotensin (Ang) II to Ang-(1–7), and Ang I to Ang-(1–9), which are cerebro-cardiovascular protective peptides (Figure 10)[74]. However, severe and critically ill COVID-19 patients face a generalized reduction/depletion of cell bearing ACE2 receptors due to infection/immunization along with soluble ACE-2 (sACE2) that, under homeostasis, are involved in the RAS would be now *de facto* likely bound to one of the Spike(S) proteins forming the corona around SARS-COV-2.[75-78]

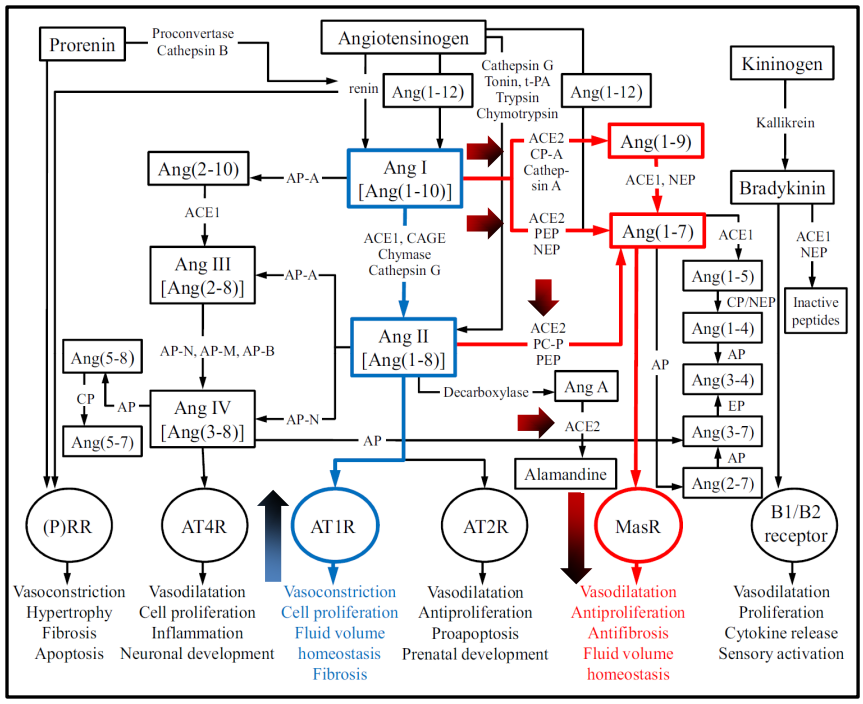

Figure 10: The renin-angiotensin system. The two main axes of RAS are highlighted with colors. ACE2-Ang (1-7)-MasR axis (red lines) counterbalances the harmful effects of the ACE1-Ang II-AT1R axis (blue lines)

Furthermore, the sympathetic and parasympathetic neuronal systems become the conduit by which SARS-CoV-2 can extend its neurovirulence. Dysregulation of the neural systems controlling cardiovascular function can lead to chronic sympa-thoexcitation and so-called "neurogenic hypertension", a key contributor to the development of cardiovascular diseases (CVD). CVD themselves may be primary or secondary to acute lung injury (ALI) as a clinical manifestation in COVID-19 patients[79].

The cardiopulmonary workload can increase which is an important consideration for patients with preexisting comorbidities[66] such as hypertension and/or heart failure (HF)[80,81]. Underlying etiology of acute HF in COVID-19 may include infarction or inflammation (myocarditis)[82], acute myocardial ischemia, acute respiratory syndrome disease (ARDS), acute kidney injury (AKI) and hypervolaemia[83]. In a study of 416 patients of whom 57 died, cardiac injury was a common finding (19.7%) as 10.6% had coronary artery disease (CAD), 4.1% HF and 5.3% cerebrovascular disease[84].

Myocarditis appears in COVID-19 patients several days after initiation of fever and is indicative of myocardial damage caused by the SARS-CoV-2 infection. The cumulative effect of myocarditis, RAS dysregulation, other CVD with/without preexisting comorbidities and ALI can only enhance a cytokine storm already in full force in the heart of critically ill patients. Fulminant in severe cases of COVID-19 but nevertheless present at various levels of intensity throughout the segregated levels of the disease, cytokine storm has been reported in CVD with increases of numerous cytokines including IL-6 IL-2, IL-7, G-CSF, CXCL10, CCL2(MCP-1) and TNFa (Figure11)[85-87].

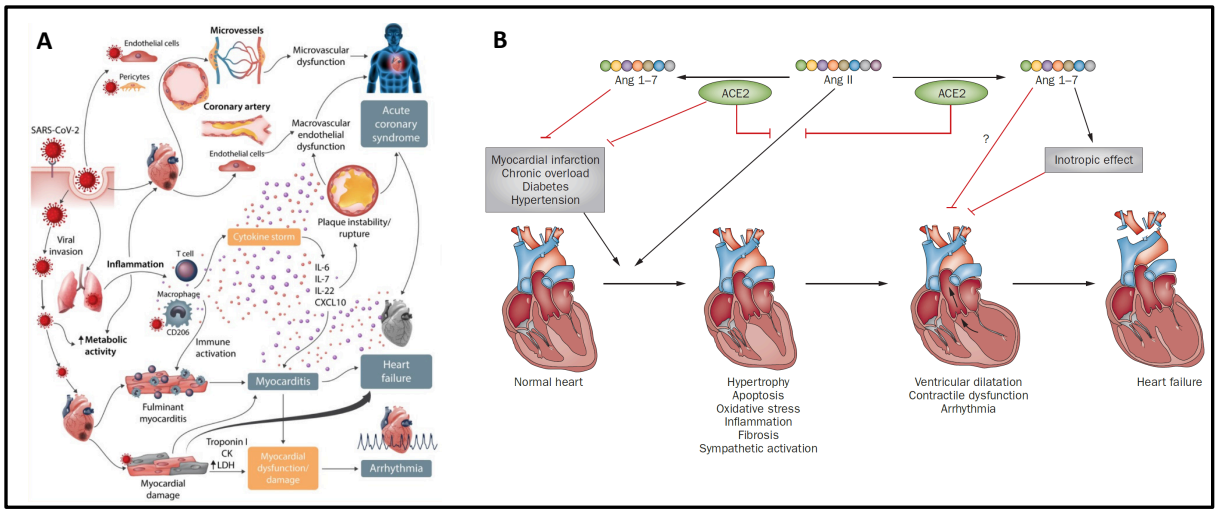

Figure 11: Highlights of cardiovascular involvement in COVID-19. Infection of endothelial cells or pericytes could lead to severe microvascular/ macrovascular dysfunction and elevated level of cytokines such as IL-6, IL-7, IL-22, and CXCL10.

Biomarkers able to convey the propensity to survive a SARS-CoV-2 infection is especially important for physicians attending critically ill COVID-19 patients. Early in the outbreak, elevated D-dimers was reported as a key differentiator of survivors and non-survivors COVID-19 patient and more recently linked to purpura fulminans "COVID-19 toes" (Figure 12)[53,88,89]. Beyond the innate immune response releasing pro-inflammatory mediators, the infection process by β-coronavirus also lead to the release of F3 (Tissue Factor/Factor III)[33] a well-recognized initiator of disseminated intravascular coagulation (DIC) in lungs[90,91]. Many viremias, including human immunodeficiency virus (HIV), varicella, hepatitis, or cytomegalovirus infections are associated with DIC[92]. Hyper and hypo fibrinolysis are the 2 types of DIC but include a broad spectrum between them[93]. Hypofibrinolysis is the typical representation of DIC; a condition in which small mobile blood clots develop throughout the bloodstream eventually blocking (microthrombus) the smaller blood vessels (microvasculature). Severe and critically ill COVID-19 patients also suffer from the inability to efficiently degrade the forming microthrombus and it was one of the key findings reported in the clinicopathology autopsies of 10 African American patients with COVID-19[94].

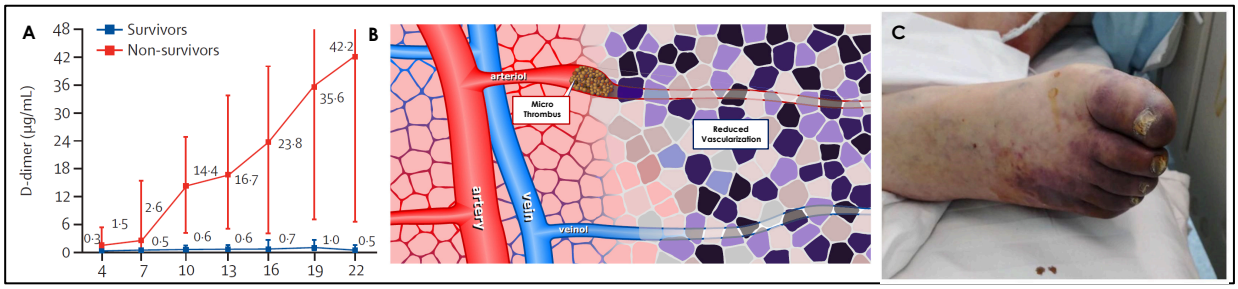

Figure 12: A) D-Dimers levels in survivors versus non-survivors. B) Schematic of microthrombus formation leading to reduced vascularization. C)COVID-19 toes.

Simplistically presented, fibrinolysis homeostasis can be viewed as the equilibrium in the converting kinetics of 2 key zymogens namely prothrombin (Factor II) and plasminogen. Infection of the cilia presenting epithelial cells by SARS-COV-2, is signaled by the release of tissue factor (F3) in conjunction with pro-inflammatory mediators. Over time, the infection severity and continuous exposure to excess F3 can exhausts the available tissue factor pathway inhibitor (TFPI), leading to rampant conversion of prothrombin to thrombin (Factor IIa), persistent feedback activation of factor XI (FXI) by the generated thrombin, hence virtually continuous fibrin and microthrombus generation. Various forms of the anticoagulant heparin have been utilized to inhibit the fibrin upstream cascade in COVID-19 patients[55].

SARS-CoV-2 "lengthy" shedding has been reported to extend as much as 37 days in some COVID-19 patients[53]. Shedding refers to the expulsion and release of virus progeny or virion; the complete, infective form of a virus outside a host cell, with a core of RNA or DNA and a capsid. The initial concern was infectivity of COVID-19 patients beyond the immunological primary immune response[60,95,96] in which the patient's immunoglobulin (IgG) are now able to detect SARS-COV-2 and contribute to its inactivation[97,98].

The methodology to detect SARS-COV-2, reverse transcriptase polymerase chain reaction (RT-PCR; One Step/Two Steps), is incapable of differentiating between ribonucleic acid (RNA) from an intact, fully virulent SARS-CoV-2 and SARS-CoV-2 RNA originating from viral debris due to the virus lysis during phagocytosis; a process occurring during/post primary immune response by which cells such as a macrophage, ingests and destroys foreign matters (Figure 12)[99]. In vivo viral RNA, single or double stand, can have exceptionally long half-lives of 6-12 hours compared to host endogenous (~2 minutes)[100]. Furthermore, infection location such as the CNS and ensuing cerebrospinal fluid (CSF) can lead to bi-phasic RNA debris prolonging the "shedding period" if reported via a RT-PCR methodology.

South Korea lead infectious disease expert, Dr. Oh Myoung-Don, confirmed that RT-PCR "…detected the RNA of the dead virus." in recovered patients. The test reported false positives not reinfections as 263 people who tested positive for a second time to SARS-CoV-2 days and even weeks after marking full recoveries were reported[101].

The false positive RT-PCR results in vaccinated/cured COVID-19 patients is further substantiated by the Chinese government intensive collection, started February 16, 2020, of convalescent plasma from vaccinated/cured COVID-19 patients in Wuhan, Hubei province, China[102]. Interestingly, February 16 2020 +22 days the President of China, Xi Jinping, was in Wuhan to disclose that COVID-19 was "curbed"[103].

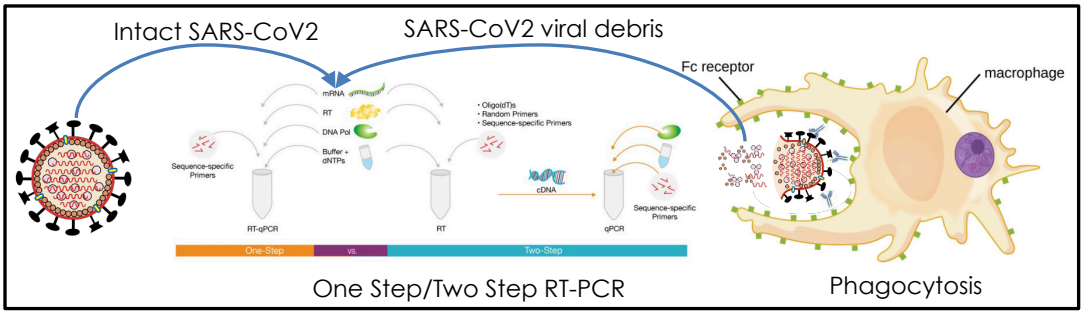

Figure 12: One Step or Two step RT-PCR cannot distinguish mRNA from intact, virulent SARS-CoV-2 and viral debris from phagocytosis of SARS-CoV-2.

As the clinical drug candidate in The Hesperidin Study, hesperidin is anticipated to prevent entry/replication of SARS-CoV-2, modulate inflammatory mediators attempting to prevent cytokine storm and potential neurological and/or cardiopulmonary injuries in COVID-19 patients.

IV. Hesperidin anticipated inhibitions mechanisms of SARS-CoV-2

The scientific and medical rationales for the use of hesperidin in The Hesperidin Study are derived from combined scientific literature reviews of reported potential therapeutic contributions of hesperidin. As such, hesperidin was reported to prevent entry and replication SARS-CoV/SARS-CoV-2 by inhibiting its intrinsic structures such as Spike(S) protein and 3CLpro. Hesperidin was also reported in the literature to downregulate the majority of the same pro-inflammatory mediators and cardiopulmonary diseases biomarkers afflicting COVID-19 patients. Furthermore, hesperidin demonstrated cognitive improvements in animal models that could lead to clinical benefits to COVID-19 patients with neurological consequences of the diseases. The extensive evidences of potential benefits in COVID-19 were compiled and lead to the development of The Hesperidin Study clinical program (Figure 13).

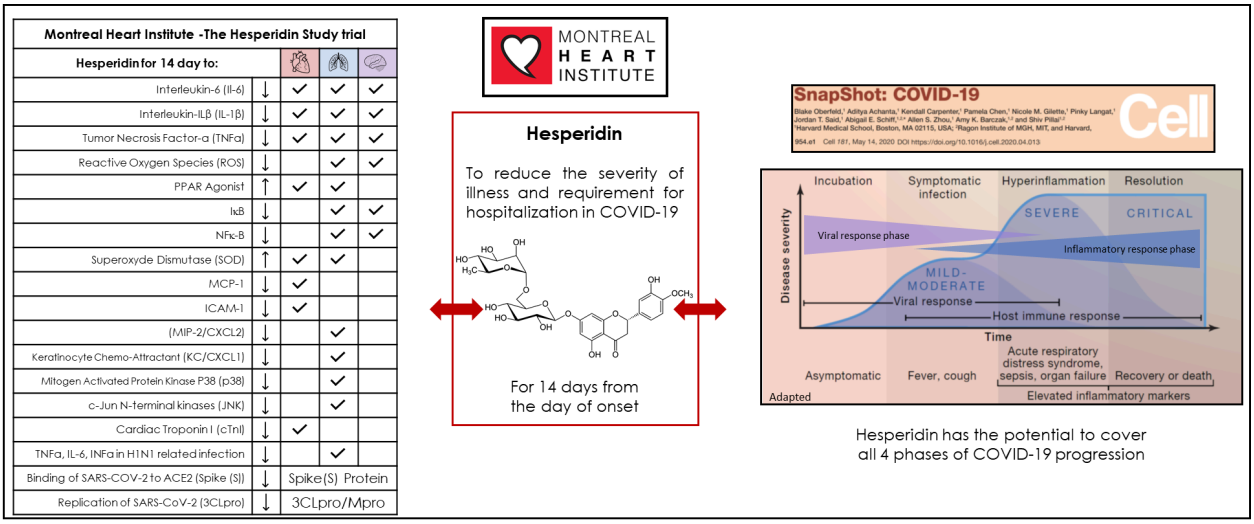

Figure 13: Overview of the potential clinical benefit of hesperidin in COVID-19 patients. Prevent entry and replication of SARS-CoV-2 by inhibiting both Spike(S) Protein and 3CLpro and modulate pro-inflammatory mediators

To date there are no treatments, vaccines or effective drug that can be used to prevent the entry and replication of SARS-CoV-2 in COVID-19 patient via an understood inhibitory mechanism. Designing pharmaceutical interventions where a host is infected/immunized with a live and virulent virus can be divided into two categories: interventions that act on the human immune system/human cells or inhibition the virus itself. Hesperidin initially became a drug candidate for a clinical trial in COVID-19 patients as it was reported to directly inhibit 2 key components of the SARS-CoV family, namely Spike(S) protein and 3CLpro. While hesperidin was isolated almost 2 centuries ago[104], the hesperidin containing Chenpi, believed to regulates ch'i (气), has been used as a common ingredient in traditional Chinese medicine for more than 10 centuries[105]. Zhang Zi-he, the famous 12th century physician of the Song Dynasty has reported the properties of Chenpi as "Chen Pi is up bearing and floating, goes to the lungs and spleen, influences the upper

(part) and frees the flow."[106]. To this day, Chenpi is extracted from tangerine peel and once aged, can sell up to 4500$/kg CAN for the more refined versions. As such, hesperidin and its versatile therapeutic benefits have been demonstrated through a plethora of clinical trials and animal models over the years as PubMed.gov tabulated over 2200 publications when hesperidin is the search word.

Hesper**idin** is a member of the flavonoid family and is composed of an aglycone moiety, hesper**etin** and a sugar moiety, rutinose, itself a disaccharide, made from L-rhamnosyl and D-glucose (Figure 14)[107]. Hesperidin can be isolated along with another flavonoid Naringin mainly from the albedo part that sits between the endocarp and exocarp of citrus sinensis (the fruit orange). Hesperidin is also present in significant amount in commercial orange juice[108].

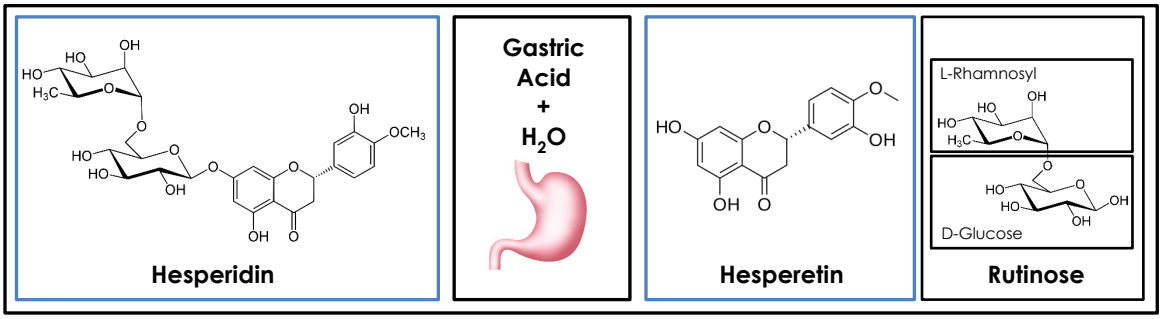

Figure 14: Structure of the flavonoid hesperidin and its aglycone hesperetin.

The scientific literature review started to focus on hesperidin as it was reported that its aglycone hesperetin directly inhibited the 3CLpro (Mpro) of SARS-CoV (2002) hence preventing possible production (replication) of virion with an IC_{50} of 8.3uM[109] and a selectivity index ~300[110].

There has been close to 300 publications with hesperidin as a key word in the last 18 months alone with over 1/3 of them published since the SARS-COV-2 outbreak in Wuhan China. Tabulation of publications regarding hesperidin cannot fully encapsulate recent literature regarding COVID-19 due to the exceptional nature of the pandemic and the speed at which publications are placed on the internet allowing scientists/medical corps to read them.

Within this massive influx of scientific/medical publications focused around SARS-COV-2 and COVID-19, computational modelling publications were the first to confirm hesperidin' potential as an inhibitor of SARS-COV-2 3CLpro[111] (Figure 15). 5 publications have now been tabulated, each confirming the replication inhibition potential[112-116]. Due to its highly conserved sequence across the SARS-CoV family, 3CLpro is an attractive therapeutic target dubbed "the Achilles' heel of coronavirus"[117].

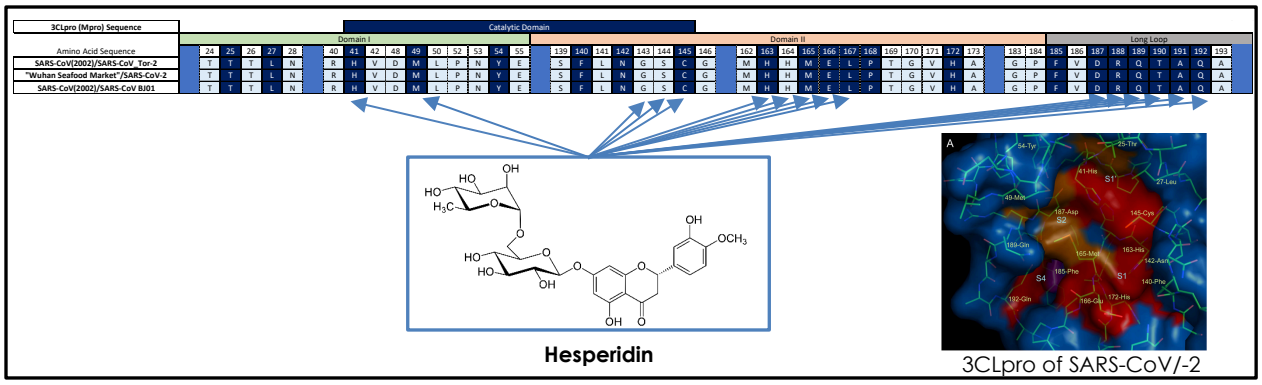

Figure 15: Representation of how hesperidin binds to SARS-CoV-2' 3CLpro catalytic site leading to prevention of viral replication

Furthermore, computational modelling publications demonstrated that hesperidin could binds the RBD of Spike(S) protein from SARS-COV-2 and, in doing so, prevent its initial interaction with ACE2 receptors ultimately leading to a prevention of entry by SARS-CoV-2[116](Figure 16).

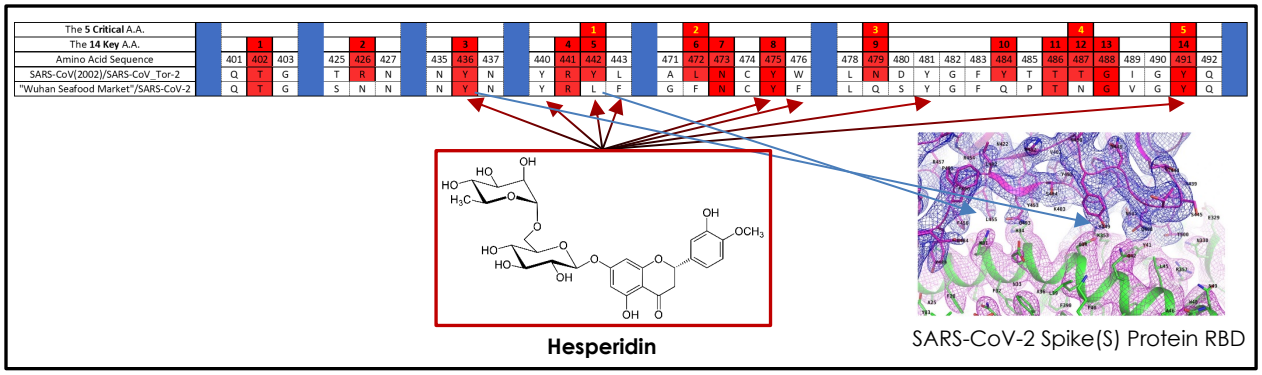

Figure16: Representation of how hesperidin binds to the region binding domain (RBD) of Spike(S) protein from SARS-CoV-2 leading to prevention of viral entry into cells expressing ACE2 receptors on their surfaces

V. Hesperidin anticipated assistance to the immune system of COVID-19 patients

The suggested interfering/inhibiting of Spike(S) protein and 3CLpro of SARS-CoV-2 could lead to a positive decrease of its viral kinetics and *de facto* dynamics (Figure 17)[118] during the COVID-19 patient' most vulnerable period of infection/immunization, the lag time phase of the immune response. As such, hesperidin could provide the infected host a short (14 days) but key window of immunomodulation to allow development of the host natural immunity culminating with the primary immunoglobulin (IGg) response against SARS-COV-2 (Figure 18)

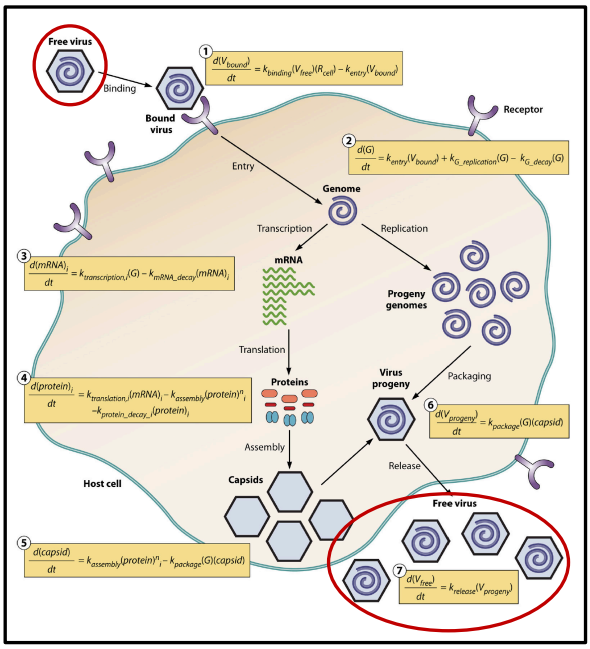

Figure 17: SARS-CoV-2 viral kinetics. Each step of reproduction can be described by a differential equation; (1) Binding, (2) Entry, (3) Transcription, (4) Translation. (5) Assembly, (6) Encapsidation and (7) Release. By inhibiting binding (Spike (S) protein) AND translation (3CLpro) hesperidin will impact or stop the kinetics leading to either a reduction or complete inhibition of the replication process.

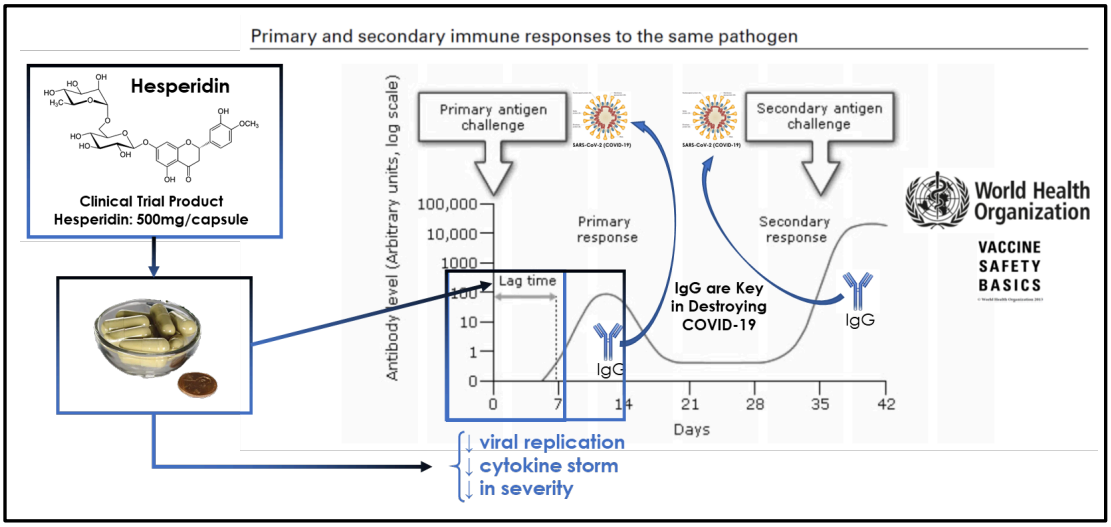

Figure18: The lag time phase of the immune response. hesperidin could provide the infected host a short (14 days) but key window of immunomodulation to allow development of the host natural immunity (primary response).

What makes hesperidin the ideal clinical candidate for The Hesperidin Study is its potential for not only prevent entry and replication of SARS-CoV-2 but, should the infection/immunization be already initiated, hesperidin can continues to have an active and quite substantial role by addressing the sequelae generated by SARS-CoV-2.

VI. Hesperidin anticipated modulation of pro-inflammatory mediators leading to a decrease of cytokine storm, cardiopulmonary injuries and severity of COVID-19

The broad therapeutic potential of hesperidin exhibited in animal models was comprehensively reviewed recently[119]. Segments addressing hesperidin role in downregulating key pro-inflammatory cytokines such as TNFa, IL-1β, IL-6, NFκB and ERK1/2 (Map2K1), were compiled and combined to a detailed representation of the biochemical paths and processes occurring in a cytokine storm. Interestingly, the anticipated benefits of hesperidin for COVID-19 patients would be independent of disease stratification (Figure 19)[119,120].

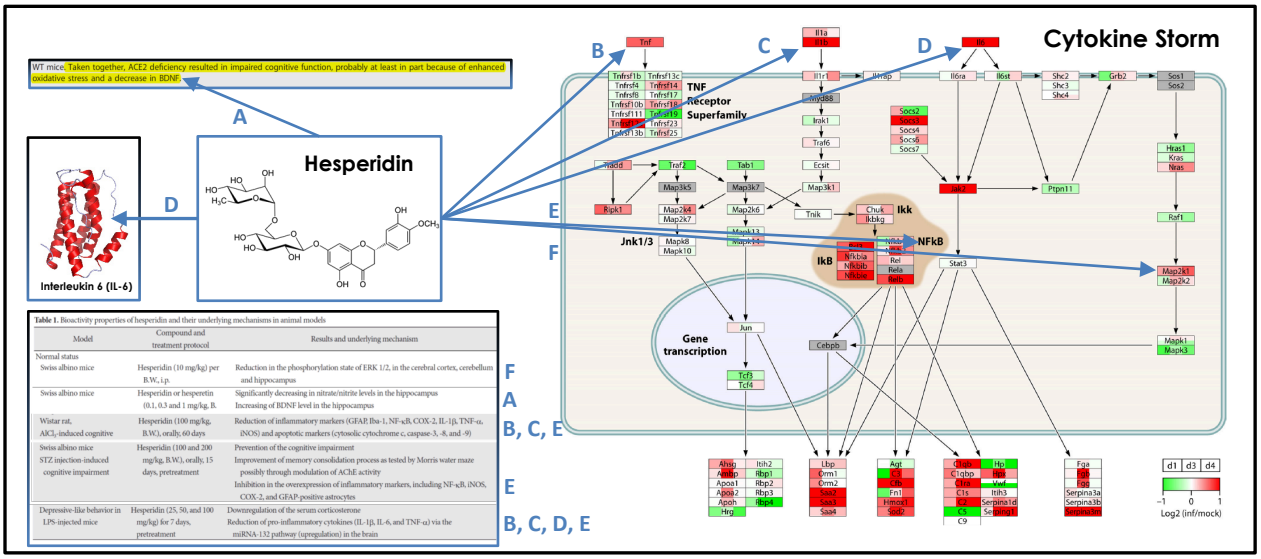

Figure19: Example of some cytokine storm biomarkers downregulated by hesperidin. The downregulation of pro-inflammatory cytokines and chemokines by hesperidin will benefit COVID-19 patients by reducing the symptoms of the infection.

As presented in section III, neurotropic and pulmonary infection by SARS-COV-2 renders the cardiopulmonary system highly susceptible to dysregulations. As a result of intense cytokine storm and severe infection, hospitalized patients with/without a history of CVD can present with dyspnea and/or acute lung injury(ALI) related to mechanical ventilator assistance or not[55,121].

Hesperidin attenuated induced lung injury in an influenza A virus (H1N1) rodent model through its anti-inflammatory effects. The pulmonary function of rats were significantly impaired, showing increased of the alveolar-arterial oxygen tension difference (P(A-a)O_2) and decreased of the oxygenation index (PaO_2/FiO_2) after a 5 day infection with H1N1. The group treated with hesperidin showed that the decreased pulmonary function was reversed in a dose-dependent manner, suggesting that, at a suitable dose, hesperidin was able to mitigate H1N1-induced lung impairment. Furthermore, Hesperidin attenuated local inflammation by inhibiting immune cell recruitment and cytokine release of pro-inflammatory cytokines including TNF-a, IFN-a, and IL-6. By decreasing the levels of those key biomarkers, Hesperidin could protect against lung injury by decreasing cytokine release from pulmonary microvascular endothelial cell (Figure 20)[122].

As presented in section II, neurotropic and potential systemic infection by SARS-COV-2 renders the cardiopulmonary system highly susceptible to dysregulations. When COVID-

19 patients require hospitalization to treat their infection, lungs and heart typically become key organs to establish severity and preferred treatment algorithm considering a *de facto* diagnosis of COVID-19. Hospitalized patients with/without a history of CVD suffer from the infection with dyspnea and ALI which result in intense cytokine storm with or without HF. Beyond the benefits vis a vis cytokine storm presented previously, hesperidin provided key benefits in an acute myocardial infarct animal model by reducing the size of the infarct in a dose dependent fashion in addition to downregulating key pro-inflammatory makers such as Il-6, CCL2 (MCP-1) and IL-1β (Figure 21)[123].

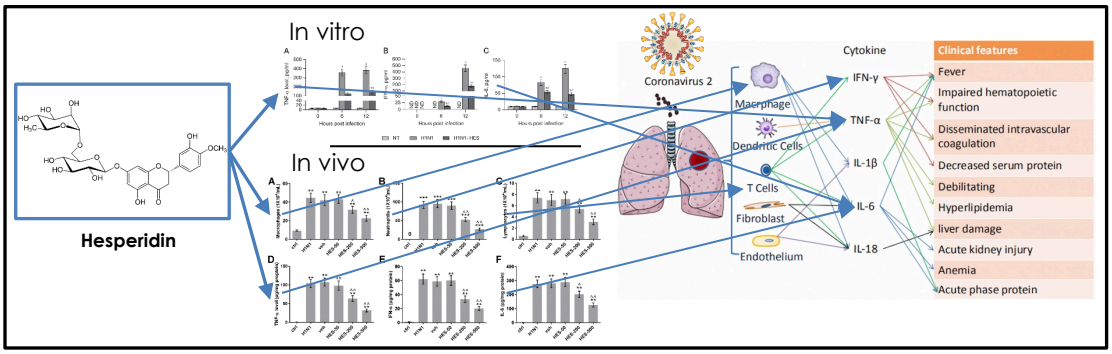

Figure 20: Hesperidin attenuated local inflammation by inhibiting immune cell recruitment and cytokine release of pro-inflammatory cytokines including TNF-a, IFN-a, and IL-6. During in vivo studies, hesperidin was reported as decreasing macrophages, neutrophils and lymphocytes.

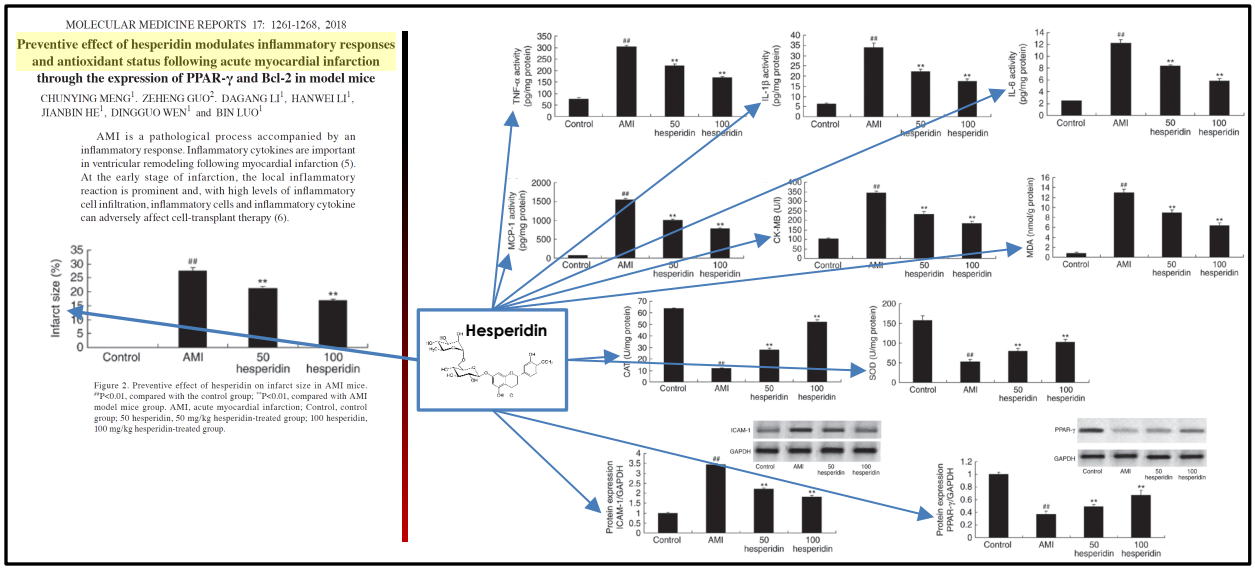

Figure21: Preventive effects of hesperidin in an AMI animal model. Hesperidin can modulate the inflammatory response created by the myocardial infarct model ultimately leading to a decrease of the infarct size.

For additional scientific support of The Hesperidin Study conducted in collaboration with the Montreal Heart Institute please review the presentations on the topic at www.ingenewpharma.com

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