Madagascar Protocol to Treat COVID 19

Two Mechanism:

Artemisia annua Targeting Ferritin & Ivermectin Stopping Viral Replication

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Abstract. In this study, the following topics are discussed in a chained analysis of events:

Hydrogen peroxide, hydrogen peroxide in the human body, hydrogen peroxide and the role of reactive oxygen species in antiviral defense, ferritin and inflammation, ferritin, inflammation and covid-19, silent hypoxia, ferritin, inflammation, and multi-organ injury in covid-19 (sudden death?), artemisia annua (artemisinin) targeting ferritin, immunoregulatory and anti-inflammatory actions of artemisinin and its derivatives, ivermectin and viral inhibition, and the Madagascar protocol with an updated analysis. The Madagascar Protocol comprises the use of Artemisia annua and ivermectin as a combination therapy to treat COVID 19. Both have proven to be successful in the treatment of the virus. This article discusses the scientific evidence that supports the protocol.

Keywords. Madagascar Protocol, Artemisia annua, Ivermectin, Ferritin, COVID-19.

Introduction

D'Alessandro et al (2020) have reported that in recent decades, drugs used to treat malaria infection have been shown to be beneficial for many other diseases, including viral infections. In particular, they have received special attention due to the lack of effective antiviral drugs for use against new emerging viruses (i.e., HIV, dengue virus, chikungunya virus, ebola virus, etc.) or against classic infections due to drug-resistant viral strains (i.e., human cytomegalovirus). They reviewed the in vitro/in vivo and clinical studies conducted to evaluate the antiviral activities of four classes of antimalarial drugs: Artemisinin derivatives, aryl-aminoalcohols, aminoquinolines, and antimicrobial drugs.

Antimalarial drugs are usually divided based on the chemical structure or the source of the drugs. Most of them derive from traditional medicine and plants. They present different modes and various mechanisms of action, which are often still not elucidated. Furthermore, due to the complexity of these

molecules, additional side activities have been reported. For these reasons, antimalarial drugs have been studied, proposed, and sometimes used for the treatment of other pathologies, such as cancer, autoimmune diseases, and non-malaria infectious diseases. Moreover, the geographic overlaps between malaria and viral-related diseases have led to the consideration of possible use of antimalarial drugs as new antiviral drugs. Finally, the lack of new effective antiviral drugs and vaccines against many viral infections has strengthened interest in the potential antiviral activity of antimalarial drugs (D'Alessandro et al 2020).

In their study, D'Alessandro et al (2020) discussed the use and the efficacy of the principal antimalarial drugs used against human viruses. These antimalarial drugs are divided into four main groups: Artemisinin derivatives, arylaminoalcohols, aminoquinolines, and antimicrobial drugs. Based on detailed documented research D'Alessandro et al (2020) concluded that the use of antimalarial drugs might be useful, especially in cases of antiviral resistance, and in light of the emergence of many viruses against which effective drugs are not available.

Regarding the effectiveness of Ivermectin, there are many examples and scientific evidence already published and made public in different communication networks. For example, a group of senior doctors with vast clinical experience met on July 19, 2020 under the aegis of Academy of Advanced Medical Education (Bombay, India). The panel looked at Ivermectin, one of the old molecules, and evaluated its use in COVID 19 (Novel Coronavirus Disease 2019) management. After a critical panel discussion, all the attending doctors came to a conclusion that Ivermectin can be a potential molecule for prophylaxis and treatment of people infected with Coronavirus, owing to its anti-viral properties coupled with effective cost, availability and good tolerability and safety (Vora, Arora, and Behera, 2020). Additionally, TrialSite (2020) recently communicated that the president of one of Dominican Republic's largest private health systems (Rescue Group), Dr. José Natalio Redondo, reported that at least 6,000 COVID-19 positive patients have been treated, with excellent results, using Ivermectin.

It has been reported that Artemisia annua and Ivermectin has been used successfully for the treatment of malaria in Africa. Coincidentally, the Madagascar Protocol comprises the use of Artemisia annua and Ivermectin as a combination therapy to treat COVID 19. Both have proven to be successful in the treatment of the virus.

This article discusses the scientific evidence that supports the efficacy of the Madagascar Protocol. The following topics are discussed in a chained analysis of events:

Hydrogen peroxide in the human body, hydrogen peroxide and the role of reactive oxygen species in antiviral defense, ferritin and inflammation, ferritin, inflammation and covid-19, silent hypoxia, ferritin, inflammation and multi-organ injury in covid-19 (sudden death?), artemisia annua (artemisinin) targeting ferritin, immunoregulatory and anti-inflammatory actions of artemisinin and its derivatives, ivermectin and viral inhibition, and the Madagascar protocol with an updated analysis.

Hydrogen Peroxide

Biocides, at a high concentration, cause massive cellular damage at a macromolecular level, with disparate mechanisms of action depending on the chemical nature of the biocide. Oxidative biocides, such as chlorine and hydrogen peroxide (H2O2) remove electrons from susceptible chemical groups, oxidizing them, and they, themselves, become reduced in the process. At a cellular level, low levels of oxidation can be a highly reversible process and prokaryotic organisms have evolved many defenses against these effects. At the proper biocide concentrations, these defense mechanisms can be overwhelmed, with significant surface cell wall and intracellular damage. Oxidizing agents are usually low molecular weight compounds and are considered to easily pass through cell walls/membranes, whereupon they are able to react with internal cellular components, leading to apoptotic and necrotic cell death. Alternatively, they can severely damage microbial structure causing the release of intracellular components, which are then oxidized (Finnegan, 2020).

Although biochemical mechanisms of action may differ between oxidative biocides, the physiological actions are very similar. Oxidative biocides are proposed to have multiple targets within a cell as well as in almost every biomolecule. These include peroxidation and disruption of membrane layers, oxidation of oxygen scavengers and thiol groups, enzyme inhibition, oxidation of nucleosides, impaired energy production, disruption of protein synthesis and, ultimately, cell death (Finnegan, 2020).

The chemistry of organic peroxides has more than a hundred-year history. Currently, organic peroxides are widely used as oxidizing agents and initiators for free-radical reactions both in industry and in the laboratory. These compounds are produced and involved in various natural and biological processes and have been explored extensively as antimalarial agents, anthelmintics, and anticancer drugs.

Currently, the progress in the chemistry of organic peroxides is mainly a result of their biological activity and pharmaceutical application. The search for effective antimalarial and antihelminthic drugs is the main challenge of medicinal chemistry of peroxides (Yaremenko et al, 2016).

Compounds with high antimalarial, antihelminthic, antitumor and antiviral activities were found among natural, semisynthetic, and synthetic peroxides. The main biologically active frame of these compounds includes five-membered 1,2-dioxolane, 1,2,4-trioxolane, and six-membered 1,2-dioxane, 1,2-dioxene, 1,2,4 trioxane cycles. The naturally occurring peroxide artemisinin and its semisynthetic derivatives, artemether, arteether, and artesunate, are applied on a large scale for malaria treatment (Yaremenko et al, 2016).

Hydrogen Peroxide in The Human Body

Peroxides are widely used in various areas of life. The traditional and the most developed field is the application of peroxides as radical initiators in industrial processes in the manufacture of polymers from unsaturated monomers: styrenes, butadienes, chlorovinyls, ethylenes, acrylates, as well as in cross-linking of silicone rubbers, acrylonitrile-butadiene rubbers, fluororubbers, polyethylene, ethylene-propylene copolymer, etc. Hydrogen peroxides are active components of antiseptics and disinfectants (Vil' et al, 2017).

It has been explained by Halliwell, Clement & Long (2000) that hydrogen peroxide (H_2O_2) is a pale-blue covalent liquid, freely mixable with water and apparently able to cross cell membranes, although the pathways it uses to traverse have not been identified. Multiple references have determined high (usually ≥50 μM) levels of H_2O_2 as being cytotoxic to a wide range of animal, plant and bacterial cells in culture, although LD50 values and the mode of cell death induced, apoptosis or necrosis, depend on the cell type used, its physiological state, length of exposure to H_2O_2, the H_2O_2 concentration, and the cell culture media employed. It is generally thought that H_2O_2 is very toxic in vivo and must be rapidly eliminated, employing enzymes such as catalases, peroxidases (especially glutathione peroxidases) and thioredoxin-linked systems.

The levels of H_2O_2 at or below 20-50 μM seem to have limited cytotoxicity to most cell types. Indeed, there is a growing research showing that H_2O_2 can be used as an inter- and intra-cellular signaling molecule. The role of H_2O_2 as a second messenger in the activation of NFkB in some, but not all, cell

types has been elucidated. Other evidence of the signaling roles for H2O2 have been found. These may be good reasons not to eliminate all the H2O2 generated in vivo, its use in physiological signaling mechanisms is important. At sites of inflammation, H2O2 generated by activated phagocytes appears to modulate the inflammatory process, e.g. by up-regulating expression of adhesion molecules, controlling cell proliferation or apoptosis and modulating platelet aggregation (Halliwell, Clement & Long, 2000).

The Fenton reaction, a process of oxidation of organic molecules by Fe and H2O2, is very common in the biological system, first described by H. J. H. Fenton in 1894. Hydrogen peroxide can contribute to Fenton chemistry not only by being one of the substrates but also by liberating iron from heme proteins and reducing iron in the inflammation process. The data presented by Halliwell, Clement & Long, 2000, emphasize the importance of metal ion sequestration in preventing the toxicity of H2O2 in vivo by decreasing the occurrence of Fenton chemistry.

Mentel' et al (1977) reported that the effect of H2O2 on adenovirus types 3 and 6, adeno-associated virus type 4, rhinoviruses 1A, 1B, and type 7, myxoviruses, influenza A and B, respiratory syncytial virus, strain long, and coronavirus strain 229E were studied in vitro, using different H2O2 concentrations and times of exposure. A 3 % concentration of H2O2 inactivated all the viruses being studied within 1--30 min. Coronavirus and influenza viruses were found to be most sensitive. Reoviruses, adenoviruses and adeno-associated virus were relatively stable. Hydrogen peroxide was found to be a convenient means for virus inactivation.

Hydrogen Peroxide and the Role of Reactive Oxygen Species in Antiviral Defense

Skulachev (1998), from Lomonosov Moscow State University, hypothesized that reactive oxygen species (ROS) including O2- , H2O2, OH-, are generated in the cell as the result of "parasitic" chemical reactions of molecular oxygen with the enzymes and coenzymes of the initial and middle parts of the respiratory chain. ROS are also generated by specific enzymes which oxidize certain substrates by O2 generating O2 -· or H2O2.

The list of pathologies associated with a dramatic increase in the level of ROS include viral infections (Akaike, Suga, and Maeda, 1998). This is not limited to the altered balance between the parasitic reactions generating ROS and ROS inactivation processes. Maeda et al. demonstrated that infection

of mice with influenza virus induces strong activation of xanthine oxidase in the lung (the rate of the xanthine oxidase reactions is increased by 2-3 orders of magnitude). A similar effect was also detected in animals infected with cytomegalovirus (Skulachev, 1998).

Xanthine oxidase is the enzyme which catalyzes oxidation of xanthine and hypoxanthine by molecular oxygen. Unlike most oxidases which generate water from O2, xanthine oxidase converts O2 into O2 - and H2O2. So, it is like NADPH-oxidase of the plasma membrane of phagocytes, which reduces oxygen to superoxide (Henderson and Chappell, 1996 in Skulachev, 1998).

In the case of phagocytes, O2 is their biological weaponry used to defend against pathogenic bacteria. Apparently, ROS has a different role in the case of a viral infection. It was shown by Akaike et al (1996, 1998) that the outburst of xanthine oxidase by itself does not suppress the production of the viruses. However, the virus can consider increased ROS as something dangerous. Certain viruses possess specific mechanisms preventing an increase in the level of ROS during infection. For example, human T-lymphotropic virus stimulates the formation of thioredoxin that is an important component of the antioxidant defense in the cell (Nakanura et al, 1995 in Skulachev, 1998). Skulachev (1996, 1997, 1998) reported that ROS are known to actively induce apoptosis. Apoptosis is one of the ways to defend against viral infection; infected cells commit suicide, thus killing the viruses.

Skulachev (1998) proposed the following hypothesis to explain the role of xanthine oxidase activation and increase in ROS during viral infection:

The initial relationship between ROS and viral infection (infection-disbalance of antioxidant defense-increase in ROS-elimination of infected cells by ROS-induced apoptosis) was probably modified during evolution so that the cell considers the appearance of a virus in the cytoplasm as a signal for ROS production. This results in increase in ROS long before this increase becomes inevitable due to cellular pathology occurring during intensive replication of the virus inside the cell. Increase in ROS should induce apoptosis in the infected cell before it becomes a source of massive infection for its neighbours. Another important consequence of the suggested mechanism should include a possibility of induction of apoptosis in the adjacent cells which are in direct contact with the infected cell and are especially prone to infection. This can result from the diffusion of one ROS, namely H2O2. Hydrogen peroxide is a small neutral molecule that easily penetrates through the biological membrane, similar to H2O. Evidently, a front of elevated concentration of H2O2 would spread significantly faster around the

infected cell than a front of viral particles formed in the very same cell. Hence, an apoptotic zone would be formed around the cell which is a potential source of viral infection. This explains the phenomenon of bystanders, i.e., the cells that are not infected with the virus, but adjacent to the infected cells, that are eliminated together with the infected cells. In humans and animals a superproduction of H2O2 occurs by xanthine oxidase in response to an intensive viral infection and it can be so potent that it induces pathological effects by itself, and the virus plays only the trigger role. This hypothesis that the cell detects a virus and responds by an outburst of enzymatically generated ROS is supported by work of Falciani et al (1992).

Participation of ROS in apoptosis induced by viral infection was demonstrated for HIV by Staal et al (1990) and Roederer (1992), and for type I human T-cell leukoma virus by Yodoi and Uchiyama (1992) and Furuke et al (1997). In the latter case, infected cells are significantly more susceptible to ROS than normal ones.

Skulachev (1998) explained that one ROS, namely H2O2, is a real signal mediator, but its role is limited to "bad news". Hydrogen peroxide informs the cell that it should commit suicide. In such situations, any danger of H2O2 as a precursor of toxic hydroxyl radicals seems unimportant because the cell is supposed to die anyway.

For Rahbari et al (2017) hydrogen peroxide is an important antimicrobial agent but is also crucially involved in redox signaling and pathogen-host cell interactions. Hydrogen peroxide (H2O2) is one of the most important cellular ROS and has crucial regulatory and signaling functions. Within cells, H2O2 can be produced by the mitochondrial respiratory chain, NADPH oxidases, through the enzymatic detoxification of superoxide radicals by superoxide dismutase. The cytotoxic effects of H2O2 are well known and H2O2 is increasingly recognized as an important regulator of signal transduction in eukaryotes. Hydrogen peroxide can act as a signaling molecule by regulating growth factors and cytokines to control cell division, differentiation, and migration. Moreover, H2O2 can diffuse through biological membranes and thus act as a long-range and fast acting signaling molecule. Furthermore, H2O2 controls protein functions of redox-sensitive proteins by selectively oxidizing cysteine reactive residues.

Ferritin and Inflammation

Kernan, and Carcillo (2017) conducted studies on the correlation of hyperferritinemia (excess of ferritin) and inflammation. These two researchers from University of Pittsburgh highlight that iron is an essential component of hemoproteins, the principle proteins of oxygen transport in the cytochrome system of the electron transport chain, liver metabolism in cytochrome p450s, as well as myoglobin and hemoglobin. As such, maintaining physiologic levels of iron is essential with deficiency leading to impairment of oxidative phosphorylation, oxygen delivery and subsequent metabolic failure.

In excess, iron can generate toxic free radicals via the Fenton reaction that directly damage cellular proteins, lipids, and nucleic acids. In Figure 1, Kernan, and Carcillo (2017) illustrated this reaction, where an occasional, but potentially damaging byproduct of aerobic metabolism, ferrous iron (Fe2+) is oxidized to ferric (Fe3+), in the presence of hydrogen peroxide, producing a hydroxyl radical and hydroxide ion. Subsequently, iron metabolism is tightly regulated and actively sequestered by cells, in part by ferritin molecules to limit induced oxidative stress.

Figure 1 shows the Fenton redox reaction. Ferrous, Fe2+ iron is readily convertible into ferric 3+ iron, along with the production of free hydroxyl radicals and hydroxide anion. These free radicals become a source of cellular oxidative stress, damaging DNA, lipids and proteins. Ferritin molecules help sequester this free iron, preventing its participation in this reaction and subsequent free radical-mediated cellular damage (Kernan and Carcillo, 2017).

Figure 1. The Fenton redox reaction

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + OH^{\cdot} + OH^{-}$$

Reference: (Kernan and Carcillo, 2017)

Free serum ferritin is increased in the setting of ongoing inflammation and there is also evidence that supports a role for ferritin in modulating the immune response, via its induction of anti-inflammatory cytokines and limitation of free radical damage. Alternatively, emerging work suggests a potential causative role for ferritin in the inflammatory pathology of disease including rheumatologic,

immunologic, malignant and infectious disorders where levels not only track disease activity but may be primary in pathology and are predictive of outcome (Kernan, and Carcillo, 2017).

Hyperferritinemia, regardless of the underlying pathology, as explained by Kernan, and Carcillo (2017), is associated with high mortality. As a marker of significant macrophage activation, individuals manifesting a hyperferritinemic phenotype show a typical pattern of reticuloendothelial system activation and multiple organ dysfunction. Patients with inflammatory conditions can present macrophage activation syndrome (MAS), including viral or bacterial sepsis, systemic inflammatory response syndrome (SIRS), inherited immunologic disorders and rheumatologic disease. All are pathobiologically linked through a pattern of extreme hyperferritinemia and elevated cytokines including TNF-α, IFN-γ, IL1-β, IL-10, IL-12, IL-6 and M-CSF. A subset of these individuals will go on to develop such extreme systemic immune activation that they manifest multiple organ dysfunction and fulfill five of the eight diagnostic criteria: fever, splenomegaly, cytopenia, elevated triglycerides or decreased low fibrinogen, elevated ferritin, low or absent NK cell activity hemophagocytosis, and increased soluble IL-2 receptor (sCD25)

Kernan, and Carcillo (2017) concluded, in their study, that ferritin may be a key marker of a pathogenic player in inflammatory pathology through its signaling as part of the innate immune response and modulation of lymphocyte function. Clinical practice supports this role, as it can be used as both a biomarker of disease progress and prognosis as well as a target for therapeutic intervention.

Ferritin, Inflammation and COVID-19

Gómez-Pastora et al (2020) reported that patients infected with the novel coronavirus, designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), develop the disease COVID-19, which can cause severe pneumonia and damage the liver, heart and kidneys. The inflammatory cytokine storm has been recognized as the primary cause of death, which is defined by the excessive and uncontrolled release of pro-inflammatory cytokines, as has been reported in other infections caused by pathogenic coronaviruses. For instance, inflammatory cytokines released by macrophages (IL-6, IL-10, and TNF-α) increase in patients with severe COVID-19 disease, resulting in damage to the lungs and other organs.

Little attention has been paid to ferritin, even though hyperferritinemia has been shown to be associated with complications in other viral diseases such as dengue fever. In order to determine if the circulating ferritin concentration could be used to predict COVID-19 progression, and to associate hyperferritinemia with the development of the cytokine storm, Gómez-Pastora et al (2020) reviewed all published studies that documented serum ferritin levels in patients with severe and non-severe COVID-19 disease, along with other inflammatory factors. Their research also included studies reporting ferritin and cytokine levels in COVID-19 survivors and non-survivors.

The studies reported ferritin concentrations of COVID-19 patients only at the time of hospital admission. It can be observed that the concentrations of ferritin are generally within the normal range (30–400 μg/L) in patients with non-severe disease (according to the National Health Commission of China guidelines for COVID-19 severity classification). However, hyperferritinemia (ferritin level > 400 μg/L), was observed in patients with severe disease on admission. In fact, the average ferritin concentration was > 800 μg/L for patients with severe disease. It was noted that ferritin levels on admission were between 1.5 and 5.3 times higher in patients classified with severe disease in comparison to patients with less-severe COVID-19 disease. The studies reported that non-survivors showed ferritin levels on admission around 1400 μg/ L, which is between 3 and 4 times higher than that observed in survivors.

The studies also reported the levels of serum cytokines such as IL-6, which are especially high on admission, in those patients developing severe disease. It was reported that both ferritin and IL-6 concentrations showed higher values in non-survivors in comparison to discharged patients throughout the clinical course and increased as the patient deteriorated. When patients began to recover, the ferritin and IL-6 concentrations decreased. This may confirm that hyperferritinemia is associated with inflammatory states in SARS-CoV-2 infection, and therefore, ferritin can be a useful parameter to predict disease severity and the extent of the cytokine storm (Gómez-Pastora et al, 2020).

Active ferritin production during the course of inflammatory diseases can occur. Macrophages, which produce cytokines and account for the majority of the immune cells in the lung parenchyma, might be responsible for the secretion of serum ferritin. Moreover, ferritin synthesis can be induced by several inflammatory stimuli including cytokines, such as IL-6. Interestingly, high IL-6 concentrations in COVID-19 patients have been correlated to disease severity. Thus, ferritin might be actively secreted at the site of infection (Gómez-Pastora et al, 2020).

A letter to the editor of Pan American Journal of Public Health, by -Vargas and Cortés (2020), reported that ferritin is a key mediator of immune dysregulation, especially under extreme hyperferritinemia, via direct immune-suppressive and pro-inflammatory effects, contributing to the cytokine storm. Fatal outcomes by COVID-19 are accompanied by cytokine storm syndrome, thereby it has been suggested that disease severity is dependent on the cytokine storm syndrome. They reviewed evidence supporting the hypothesis that ferritin levels might be a crucial factor influencing the severity of COVID-19.

Vargas and Cortés (2020) highlighted a study with 20 COVID-19 patients that showed individuals with severe and very severe COVID-19. They exhibited increased serum ferritin level, with serum ferritin in the very severe COVID-19 group significantly higher than in the severe COVID-19 group, 1006.16 ng/ml vs 291.13 ng/ml, respectively. They also identified another study revealing that in patients who died of COVID-19, ferritin levels were high upon hospital admission and throughout the hospital stay. The median values of serum ferritin levels after day 16 of hospitalization exceeded the upper limit of detection in these patients, suggesting that ferritin levels increased non-stop.

It was concluded by Vargas and Cortés (2020) that serum ferritin levels were closely related to the severity of COVID-19. Finally, they reported that laboratory findings in patients with severe COVID-19 showed data consistent with cytokine storm involving elevated inflammatory markers, including ferritin, which has been associated with critical and life-threatening illness.

Abobaker (2000) reported strikingly high levels of ferritin in patients with the novel coronavirus disease 2019 (COVID-19). Garrick and Ghio (2020 in Abobaker, 2000) explained that inflammation induced by COVID-19 infection increases the hepcidin level, the main regulator of tissue iron store. It has been proposed that the coronavirus (SARS-CoV-2) spike protein has hepcidin-like action, which means that the virus can directly increase ferritin level regardless of the inflammatory effect.

A high ferritin level has been linked with poor prognosis in COVID-19. The level of ferritin in COVID-19 non-survivors is higher than that of the survivors by twofold. Intracellular iron generates reactive oxygen species in the lung by interacting with oxygen molecules which could predispose to the development of adult respiratory distress syndrome (ARDS) (Edeas, Saleh, and Peyssonnaux, 2020 in Abobaker, 2000). Intracellular iron and hyperferritinemia increase the risk of coagulopathy and oxidative stress and induce endothelial inflammation which could predispose to disseminated coagulation and

multiorgan failure (Garrick and Ghio, 2020; (Edeas, Saleh, and Peyssonnaux, 2020, in Abobaker, 2000). It seems that hepcidin antagonists could offer a potential future possible approach in supportive management of COVID-19. Iron-containing enzymes are required for viral replication, including coronavirus. It is noted that coronavirus replication was suboptimal in iron-depleted cells compared with iron replete cells (Liu et al, 2020 in Abobaker, 2000).

Huang et al (2020) performed a comprehensive systematic literature search through electronic databases. The outcome of interest for their study was the composite poor outcome, which comprises mortality, acute respiratory distress syndrome, need for care in an intensive care unit, and severe COVID-19. A total of 5350 patients were pooled from 25 studies. Huang et al (2020) found that a higher serum ferritin level was independently associated with acute respiratory distress syndrome, mortality, and severe COVID-19. This may lead to the notion of the presence of secondary hemophagocytic lymphohistiocytosis (sHLH) in COVID-19. Hemophagocytic lymphohistocytosis is a condition of hyperinflammation characterized by a cytokine storm causing fatal multi-organ failure. This condition is most commonly triggered by viral infections, which might lead to a hypothesis of SARS-CoV-2 inducing this hyperinflammatory syndrome. This meta-analysis showed that an elevated ferritin factor was associated with a poor outcome in COVID-19.

Silent Hypoxia, Ferritin, Inflammation and multi-organ injury in Covid-19 (Sudden Death?)

Cavezzi, Troiani and Corrao (2020) reported that the Coronavirus disease-19 (COVID-19) has been regarded as an infective-inflammatory disease, which affects mainly lungs, but also recently, a multi-organ involvement has been detected, with different pathways of injury. They suggested that a hemoglobinopathy, hypoxia and cell iron overload might have a possible additional role.

In this scenario, Cavezzi, Troiani and Corrao (2020) pointed out two potential pathophysiological mechanisms: (1) Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV- 2) interaction with hemoglobin molecule, through CD147, CD26 and other receptors located on erythrocyte and/or blood cell precursors; (2) Hepcidin-mimetic action of a viral spike protein, inducing ferroportin blockage.

In addition, Cavezzi, Troiani and Corrao (2020) presented the following pathologic metabolic pathways, derived from hemoglobin denaturation and iron metabolism dysregulation, as highlighted: (1) Decrease of functioning hemoglobin; (2) Iron overload in cell/tissue (hyperferritinemia); (3) Release of free toxic

circulating heme; (4) Hypoxemia and systemic hypoxia; (5) Reduction of nitric oxide; (6) Coagulation activation; (7) Ferroptosis with oxidative stress and lipoperoxidation; (8) Mitochondrial degeneration and apoptosis

Concerning lung consequences, a systemic hypoxic state, with normal pulmonary tissue compliance, has been highlighted in up to 80% of intensive care unit (ICU) patients exhibiting respiratory distress, which led a few authors to question Acute Respiratory Distress Syndrome (ARDS) diagnosis. A type of silent hypoxia is described in these patients, where they show progressively worse hypoxemia associated with normal CO2. Normocapnia reflects normal pulmonary gas exchange. The primary sensor for respiratory distress is CO2 elevation. When CO2 increases, patients show relevant respiratory symptoms at later stages only. Lastly, hyperferritinemia progressively affects alveolar-capillary/cell membrane integrity/permeability. Ultimately, inflammation, edema and lung cell necrosis may complicate the pulmonary condition (Cavezzi, Troiani and Corrao, 2020).

By mimicking hepcidin action, SARSCoV-2 might remarkably increase circulating and tissue ferritin (mainly affecting liver, spleen, bone marrow and muscles), while inducing serum iron deficiency and lack of hemoglobin, by consequence. Cell iron overload is tolerated up to a threshold, as with silent hypoxia (COVID-19 first phase). The increasing ferroptosis-linked multi-organ oxidative stress can precipitate the inflammatory/immune over-response (Interleukine storm) in the later, most critical stages. Recent laboratory data showed a relevantly lower hemoglobin level and higher ferritin levels in non-surviving patients, over the survivors. Hyperferritinemia may induce a series of direct and indirect (via autoimmunity) injuries to most organs during COVID-19, such as coagulopathies, macrophage activation syndrome, hemochromatosis-like liver injury, and other ferroptosis-driven syndromes (Cavezzi, Troiani and Corrao, 2020).

Viruses generally increase iron deposit, to favour their diffusion in host cells; conversely, our immune system tends to control iron metabolism in case of infection, also through transferrin. This key-factor of iron metabolism has ubiquitous receptors, which are used by many viruses to enter host cells. Possibly, future research could elicit the transferrin receptor as another target of SARS-CoV-2 (Cavezzi, Troiani and Corrao, 2020).

Cavezzi, Troiani and Corrao (2020) concluded that several organs are directly, or indirectly targeted by SARS-CoV-2 and multiple pathomechanisms can be described to be immune/inflammatory type and

linked to hypoxia and ferroptosis. Thromboembolism also seems to play a relevant role in later stages. Overall, pathophysiological pathways seem to overlap in most cases. They found hemoglobinopathy and iron dysmetabolism may induce a series of biological events, which objectively relate to the clinical syndromes highlighted during COVID-19.

Whether the original pathologic viral process begins in the lungs, with consequent general anemic hypoxia and iron dysmetabolism, or vice versa, hemoglobin/iron dysmetabolism is the leading process that results in multi-organ disease and further hypoxia, is a matter of urgent research (Cavezzi, Troiani and Corrao, 2020).

Perricone et al (2020) studied COVID-19 as part of the hyperferritinemic syndromes and the role of iron. It is well known that ferritin serves to bind iron molecules and to store iron in a biologically available form for vital cellular processes while protecting proteins, lipids and DNA from the potential toxicity of this metal element. It has been shown that ferritin has different implications during inflammation. Ferritin and its subunits, light chain ferritin (LHC) and heavy chain ferritin (HFC), showed in vivo and in vitro immunomodulatory effects. Despite the acute rise of blood value of ferritin as part of the normal systemic response to inflammation, a hyperferritinemic response is associated with a significantly increased mortality in septic patients. Most probably, the synthesis of ferritin may be regulated by different inflammatory cytokines such as IL-1β and IL-6 and serum ferritin is affected by upregulation of hepcidin whose production, in turn, is stimulated by pro-inflammatory cytokines, particularly IL-6.

Another variable to be considered in viral infections is the impact of iron overload. Iron is required for viral replication and other processes including mitochondrial function, ATP generation, DNA/RNA synthesis and repair and cell survival/ferroptosis. For instance, the activity of the helicases of the SARS-CoV for viral replication requires ATP hydrolysis that in turn needs the presence of iron. Iron overload leads to a worse prognosis in viral infections and iron supplementation increases the mortality in the patients, irrespectively of the anemic status. It is likely that SARS-CoV-2 requires iron for viral replication and for its function (Perricone et al, 2020). This is among the rationales for Artemisia annua therapy in COVID-19.

Perricone et al (2020) concluded in their studies that COVID-19 may be part of the hyperferritinemic syndrome spectrum. This is possible because acute iron overload is caused by the rapid synthesis of ferritin exceeding its iron incorporation rate. As a consequence of the pathogenic scenario linking iron,

inflammation and infection, there is the need to find a possible therapeutic strategy to prevent cytokine release syndrome in patients with COVID-19.

Artemisia annua Targeting Ferritin

According to Haynes et al (2013), the isolation of artemisinin from the traditional medicinal herb qīng hāo (Artemisia annua), its characterization as a peroxide and preparation of the derivatives dihydroartemisinin, artemether and artesunate, in the 1970s and 1980s by Chinese scientists under the umbrella of Project 523, collectively represents one of the great events in medicine in the latter third of the 20th Century.

This collective information is used as a counterpoint to screen the validity of two of the prevailing hypotheses of drug action of artemisinins and synthetic peroxides. Namely (1). The 'C-radical hypothesis' wherein the peroxide undergoes 'bioactivation' by ferrous iron to generate C-radicals that are thought to be the cytotoxic agents and (2).The 'heme hypothesis' wherein ferrous heme may generate either the same type of 'cytotoxic' C-radical, or the peroxide forms heme adducts, that apparently inherit the exquisite cytotoxicities of the parent peroxide in one way or another.

In general, little is precisely understood, as opposed to widely assumed, for the mechanism of drug action of artemisinins and their synthetic peroxide analogue. Ali et al (2018) have described what is called the "artemisinin activation theory". According to this theory, artemisinin is involved in an activation to generate free radical species before its activation. This hypothesis is supported by the fact that artemisinin interacts with hemoglobin-bound iron through a covalent reaction for its activation. However, later, it was assumed that ferrous heme (heme-Fe2+) may be the most competent activator of artemisinin. Artemisinin activation models were categorized into two main groups: 1. Reductive scission model and 2. Open peroxide model.

In reductive scission, ferrous-heme/non-heme exogenous Fe2+ is first attached to artemisinin by a covalent bond, causing the reductive scission of the endoperoxide bridge. This leads to the generation of oxygen-centered radicals, which subsequently self-arrange to give carbon-centered radicals. In addition, iron–peroxide interaction occurs in different ways to form either primary carbon-centered radicals (via C3–C4 bond scission) or secondary carbon-centered radicals (via 1,5 H-shifts).

The open peroxide model, on the other hand, suggests that the endoperoxide group of artemisinin produces secondary carbon-centered radicals via a Fenton reaction involving the Fe2+ of hemoglobin.

The “artemisinin activation theory” has been supported by research findings showing that artemisinin activity was significantly reduced in the presence of free radical scavengers and antioxidants, but enhanced in the presence of pro-oxidants (Ali et al, 2018). This is an important occurrence for a combination treatment with high dose vitamin C, which acts as a pro-oxidant.

It has been found that artemisinin displays anti-inflammatory activity via inhibition of NF-κ B activity and NALP3 inflammasome activation in mouse models. Artemisinin treatment attenuates the release of TNF-α, IL-1β, and IL-6 through inhibition of the NF-κ B canonical pathway, therefore demonstrating the capacity for inhibition of inflammation (Ali et al, 2018).

Tsuda et al (2018) studied the mechanisms of the pH- and Oxygen-Dependent Oxidation Activities of Artesunate, and they found that artemisinin derivatives report inhibition of hypoxia-inducible factor-1α (HIF-1α) activation, and direct DNA injury. In addition, a reactive oxygen species (ROS) generation is involved in many cases. The ROS generated by the coexistence of iron (II), artesunate, and molecular oxygen was a hydroxyl radical or hydroxyl radical-like ROS. Artesunate can reduce iron (III) to iron (II), which enables generation of ROS irrespective of the iron valence. They found that reduction from iron (III) to iron (II) was activated in the acidic rather than the neutral region and was proportional to the hydrogen ion concentration.

The mode of action of artemisinin depends on activation by cleavage of the endoperoxide bridge. There are studies that have indicated that ferrous heme, hemin, free ferrous iron, and other iron-containing species are strong activators of artemisinin. It was also found that mitochondria were directly involved in both the activation and action of artemisinin, thus further linking artemisinin action to reactive oxidative species (ROS) production and oxidative damage. Artemisinin activation is dependent on a heme-rich environment. For these reasons, the potential applications of artemisinin in anti-inflammatory and anti-viral roles, among others, have been explored in earnest over the years (Wang et al, 2019).

Recent work has closely linked artemisinin-induced cytotoxicity to oxidative damage and lysosomal function, with a focus on the role of iron in contributing to the iron-dependent form of cell death known as ferroptosis. Lysosome-mediated degradation of ferritin under autophagy conditions (termed

ferritinophagy) releases free ferrous iron, which in turn contributes to both ferroptosis and iron-mediated generation of ROS. Autophagy itself is a cellular process that is reportedly activated by artemisinin. It is clear that the relationship between autophagy, lysosomal activity, free ferrous iron, and iron dependent ferroptotic cell death following artemisinin exposure represents a major area of research in the mechanism of artemisinin (Wang et al, 2019).

Yang et al (2014) demonstrated a novel mechanism for the mode of action of artesunate. Artesunate accumulates in lysosomes and reacts with lysosomal iron. The activated artesunate then promotes lysosomal function via enhancing V-ATPase assembly. One major source of iron for the cytotoxicity of ART is attained from the degradation of ferritin by lysosomes.

Interestingly, Yang et al (2014) found that artesunate preferably accumulates in the lysosomes and is able to activate lysosomal function via promotion of lysosomal V-ATPase assembly. Furthermore, we found that lysosomes function as the upstream of mitochondria in reactive oxygen species (ROS) production. Importantly, we provided evidence showing that lysosomal iron is required for the lysosomal activation and mitochondrial ROS production induced by ART.

The study of Yang et al (2014) demonstrated that artesunate treatment activates lysosomal function and then promotes ferritin degradation, subsequently leading to the increase in the lysosomal iron which is utilized by artesunate for its cytotoxic effect. In conclusion, intracellular iron and ferritin degradation is essential for artesunate-induced lysosomal activation and cell death.

Immunoregulatory and Anti-Inflammatory Actions of Artemisinin and its Derivatives

Shi et al (2015) describe artemisinin as a sesquiterpene lactone containing peroxide bridge. For them, T-cells play a pivotal role in the acquired immune reaction, which includes three fundamental steps. First, TCR cross-linking drives T-cells from G0 to G1 transition and subsequent secretion of T-cell growth factor IL-2 and expression of high-affinity receptor IL-2Rα chain (CD25). Second, through autocrine/paracrine proliferative loop, IL-2 induces clone expansion and maintains survival of activated T-cells. Third, after successful clearance of the pathogen, the stimulus for cytokines production is lost and activated T-cells thus will undergo apoptosis.

However, in autoimmune diseases, due to the persistence of autoantigen, autoreactive T-cells will be activated and survive better. Autoreactive T-cell proliferation is involved in the pathogenesis of various autoimmune diseases, such as rheumatoid arthritis (RA) and multiple sclerosis (MS). Artemether is a potent antimalarial drug. In 2007, Wang et al. found artemether significantly suppressed the proliferation and IL-2 and interferon-γ (IFN-γ) production of T-cells triggered by TCR engagement. Artemether significantly inhibited TCR engagement-triggered MAPKs signaling pathway including phosphorylation of ERK1/2, Jnk, and P38. Authors further identified that artemether seriously affected the function of T-cells, rather than the antigen-presenting cells (APCs) to exert the immunosuppressive effects (Shi et al, 2015).

In their study, Shi et al (2015) concluded that artemisinin derivatives perform immunosuppressive functions primarily through inhibiting pathogenic T-cell activation, suppressing B cells activation and antibody production, and expanding regulatory T-cells ; the impact of artemisinins and derivatives on different immune cells is shown in figure 2, Shi et al (2015) deem that, as anti-inflammatory agents, artemisinin derivatives possess advantages to act on multiple checkpoints within the immune signaling cascade, with selectivity for activated pathogenic T-cells, to create a synergistic treatment effect on disease activity. Thus, these artemisinin derivatives may be promising candidates to treat inflammation and autoimmune disorders.

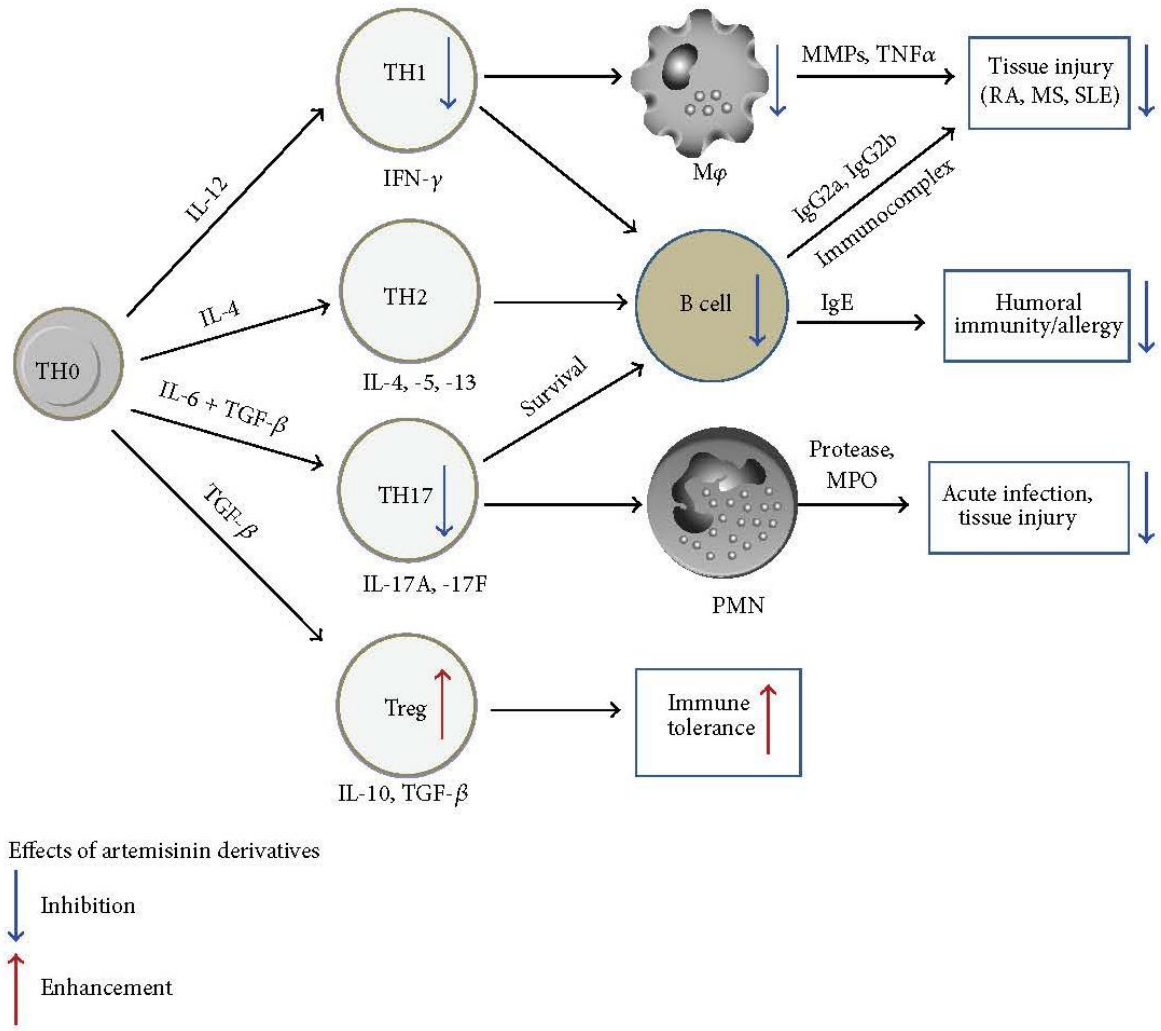
Gendrot et al (2020) conducted a study aimed to evaluate the antiviral activity of ACT at concentrations consistent with those observed in human plasma when ACT is administered at oral doses for uncomplicated malaria treatment. In their estimations of the % of inhibition of the SARS-CoV-2 replication by fixed-doses of ACT, they found that Mefloquine-artesunate exerted the highest antiviral activity with inhibition of 72.1 %.

These in vitro results presented by Gendrot et al (2020) reinforce the hypothesis that antimalarial drugs would be effective as an anti-COVID-19 treatment. Based on their results, it would be expected that countries commonly using ACT report fewer cases and fewer deaths during malaria season.

It is imperative to evaluate the ACT efficacy clinically to treat COVID-19, particularly that of mefloquine-artesunate, and the potential intervention of ACT against SARS-CoV-2, by comparing its antimalarial use and the dynamics of COVID-19, country by country (Gendrot et al, 2020).

Augustin et al (2020) reported that beyond its antimalarial effects, drug repurposing with artesunate has shown cytotoxic effects against viruses, fungi, and a variety of cancers as well as powerful anti-inflammatory effects. Several in vitro and in vivo models have demonstrated protective effects of artesunate against multiple organ failure in models of lung, myocardial and renal injury via modulation of key pro-inflammatory pathways. Severe COVID-19 disease results in the generation of pro-inflammatory cytokines, including IL-6 and IL-1b, via the toll like receptors, resulting in the production of active mature IL-1b, which is a mediator of fever, lung inflammation and fibrosis. There is a correlation between IL-6 peak levels and severity of pulmonary complications.

Figure 2. Immunoregulatory and anti-Inflammatory actions of artemisinin and Its derivatives



Reference: Shi et al (2015)

Augustin et al (2020) concluded that the hallmark of severe COVID-19 infection is a severe inflammatory response caused by a cytokine release syndrome of which pro-inflammatory cytokine IL-6 is a key component. Respiratory distress syndrome, myocarditis and renal failure are cytokine release syndrome/ cytokine storm sequelae with devastating effects. Artesunate is able to modulate pro-inflammatory cytokine pathways, and in doing so prevent multi-organ failure in models of lung, myocardial and renal injury. A safe and affordable treatment that could prevent patients with mild or moderate COVID-19 infection progressing to severe infection, as a result of cytokine release syndrome/ cytokine storm, would represent a significant breakthrough globally.

Ivermectin and Viral Inhibition

On April 3, 2020, a famous scientific publication by Caly et al (2020) was available online. It reported that ivermectin, an FDA-approved anti-parasitic, previously shown to have broad-spectrum anti-viral activity in vitro, is an inhibitor of the causative virus, SARS-CoV-2. A single addition of ivermectin to Vero-hSLAM cells, 2 hours post infection with SARS-CoV-2, was able to effect ~5000-fold reduction in viral RNA at 48 h.

Since that publication of Caly et al (2020), an overwhelming amount of scientific studies and testimonies around the entire globe have been reported about the efficacy of ivermectin. Here, a representative report by Formiga et al (2020) of some of the work being done in Brazil is presented:

In light of the potential of ivermectin to prevent replication in a broad spectrum of viruses, Rocha Formiga et al (2020) have discussed the inhibition of importin α/β1-mediated nuclear import of viral proteins as the probable mechanism underlying its antiviral activity. Since SARS-CoV-2 is an RNA virus, a similar mechanism of action may take place. A possible ionophore role for ivermectin has also been reported. Since ionophore molecules have been described as potential antiviral drugs, ivermectin could ultimately induce an ionic imbalance that disrupts the potential of the viral membrane, thereby threatening its integrity and functionality.

Formiga et al (2020) have illustrated that the pathology of COVID-19 is characterized by the rapid replication of SARS-CoV-2, triggering an amplified immune response that may lead to cytokine storm, which frequently induces a severe inflammatory pulmonary response. Disease progression may result in progressive respiratory failure arising from alveolar damage and can lead to death. Moreover, the

monitoring of SARS-CoV-2 viral load in the upper respiratory tract and bronchoalveolar lavage fluid (BALF) in patients with severe disease indicates higher loads, as well as greater viral persistence.

Regarding its anti-inflammatory properties, ivermectin has been shown to mitigate skin inflammation. Importantly, ivermectin significantly diminished the recruitment of immune cells and cytokine production in BALF assessed in a murine model of asthma. A study evaluating the ability of ivermectin to inhibit lipopolysaccharide (LPS)-induced inflammation revealed significantly decreased production of TNF-alpha, IL-1ss and IL-6 in vivo and in vitro. Further studies may establish the role of ivermectin in the inflammatory response caused by SARS-CoV-2. Besides the antiviral activity ivermectin could play a supportive adjuvant role facing the hostile infection microenvironment (Rocha Formiga et al, 2020).

Ivermectin Mode of Action

Gupta, Sahoo and Singh (2020) have reported that recently, the antiviral function of ivermectin has been discovered, which appears to be intriguing. Already its effectiveness against certain flavivirus (dengue fever, Japanese encephalitis and tick-borne encephalitis virus) and chikungunya virus has been demonstrated in vitro. Since then, the same activity has been assessed in numerous other viral infections. Currently, its potency has been recognized in eliminating coronavirus in vitro. The exact mechanism to which this effect can be attributed is yet to be validated. The speculated mechanism is inhibition of importin α/β1 mediated transport of viral proteins in and out of the nucleus. Importins, types of karyopherins, exemplify a major class of soluble transport receptors which are involved in nucleo-cytoplasmic transit of various substrates. The speculated inhibitory action of ivermectin on importin α/β1 mediated transport system explains the role of ivermectin in eliminating Covid-19 (Mastrangelo et al, 2012, Varghese et al , 2016, Tessier et al, 2019, Oka &Yoneda, 2018, Gupta, Sahoo and Singh, 2020).

In a single in vitro study, the efficacy of ivermectin against coronavirus was demonstrated by Caly et al.(2020). The in vitro potency of ivermectin against Covid-19 virus is evidence that this drug can be utilized to manage patients infected with SARS-CoV-2. Upon comparison, Ivermectin may prove to have leverage over the other pharmacotherapeutic options for the management of Covid-19. Furthermore, the treatment regimen with Ivermectin is very cost-effective. Considering these merits, it becomes imperative that multiple clinical trials with Ivermectin be conducted (Gupta, Sahoo and Singh, 2020).

The Bangladesh Protocol for Ivermectin

Prof. Mohammed Tarek Alam, Professor and Head of Department of Medicine, Bangladesh Medical College, was the lead author of this protocol. Alam et al (2020) carried out a prospective study in which a combination of Ivermectin and Doxycycline was evaluated therapeutically to treat COVID-19 patients. 100 COVID-19 patients were enrolled in the study with a predefined inclusion and exclusion criteria. RT- PCR of the SARS-CoV-2 were done at designated government hospitals. The clinical features and responses to treatment were recorded according to a dedicated protocol.

Patients were given a combination therapy of Ivermectin and Doxycycline along with supportive medical treatment. The dose of Ivermectin was 0.2 mg/kg as a single dose. Doxycycline 100 mg was given once daily for 10 days (Alam et al, 2020).

This observational study, consisting of 64 males and 36 females, was conducted from April to May 2020 in Bangladesh Medical College. The oldest patient was 84 years and the youngest was 8 years, with most patients between the ages of 21 to 40 years. Patients were divided into 3 groups: Mild (73), Moderate (20) and Severe (7), based on their symptoms. From the severe patients, 3 had fever higher than 103 degrees Fahrenheit for seven days with severe cough and lung infiltrates, 3 had severe diarrheal and 1 had uncontrolled diabetes. Of the rest, 20 patients had moderate symptoms of mild fever (100 degrees Fahrenheit) and mild cough. Moreover, 73 had mild symptoms of malaise, sore throat, loss of smell, loss of taste, and body ache. Fifty percent symptomatic improvement of mild to moderate patients was seen between the 3rd to 5th day after starting treatment. By the 7th day of treatment, all 7 severe patients' symptoms subsided by 50 percent. Retesting was done between 4 - 18 days of starting medication. Twenty-five patients underwent retesting between the 4 - 8 days, 51 between the 9 -13 days and 24 between the 14 -18 days from starting medication. All the patients tested negative. None needed intensive care admission and no deaths were reported. No toxicity was seen with the drug at any point of time (Alam et al, 2020).

Dr. Borody's Ivermectin Protocol

News Corp media is the latest major media to report on the proposal of Professor Thomas Borody. This gastroenterologist received credit for developing the world's first peptic ulcers cure, saving many lives in the process. He is proposing 'making Ivermectin available for at least those economically

disadvantaged, vulnerable individuals, infected with COVID-19, without health care access, in an endeavor to reduce the severity and duration of the novel coronavirus'. Professor Borody stepped up to publicly declare this need, despite a great majority of health authorities who do not think much on this topic. A few clinical trials have been completed (Bangladesh and Iraq), but because they have been on the smaller scale and TrialSite suspects (and this is just a speculation), because they originate out of low-and middle-income countries (LMICs) health regulators and research elites in wealthier countries are not paying attention. A real-world, observational off label initiative was deemed successful in Broward County U.S., but no medical journals are willing to consider a review of the findings. Dr. Borody broadcasted his concerns due to the complete lack of intellectual curiosity exhibited by a majority of the world's leading research agencies and health authorities (TrialSite, 2020).

In the meantime, Shannon Molloy from *News Australia* was given the green light to write about Ivermectin. *TrialSite* emphasizes this because a good many highly respected journalists working for major media will not, at least up until this point, with no benefit from such a decision. The Sydney-based

Dr. Borody, now urges health authorities to consider an Ivermectin plan for at least A) low-and middle-income countries and B) the underdeveloped areas within developed countries (TrialSite, 2020).

Molloy reports that Dr Borody believes the "answer to Australia's COVID-19 crisis" is what was termed the Australian combination of Ivermectin, Doxycycline, and Zinc. Dr. Borody, a well-established and prominent figure suggests at least in Australia: A) these medicines are already approved by authorities and proven safe and B) they do not need to go through any more preclinical research, or for that matter clinical trials unless they are to be combined in a capsule (TrialSite, 2020).

Dr. Borody is the Study Director of a Clinical Trial of Combination Therapy to Treat COVID-19 Infection. Patients in this trial will undergo treatment for 10 days with either a combination of therapies or placebo. They will then be followed for 6 months. The intervention therapy is: Ivermectin, Doxycycline Hcl, Zinc, Vitamin D3, Vitamin C.

Dr. Camargo Ivermectin Protocol

Dr. Antonio Camargo, Scientific Director of the Institute ONKOS, conducted a study on the use of high doses of ivermectin in the treatment of infection by SARS-CoV2 (COVID-19), as a case of molecular

resolution. He presented his experience and personal testimony about the use of Ivermectin to treat himself. In his case, the treatment protocol, considering the high viral load presented in the molecular test, augured a prognosis quite reserved and critical. Departing from this delicate situation, recovering completely, the protocol was formulated as follows: 60 mg of Ivermectin for 4 days, followed by 30 mg for 3 days, for a total of 330 mg in 7 days (Camargo, 2020).

Three days after starting treatment with 60 mg dose of Ivermectin daily, and after testing, it was observed that the viral load was completely negative, indicating complete disappearance of the pathogen after 3 days of treatment with this medicine (Camargo, 2020).

In this regard, sub-doses of Ivermectin should not be used, since this can cause the false impression of achieving an effect. In any case, it merits to bet on the maximum tolerated and suggested doses in order to eradicate the virus effectively and achieve rapid rates of cure (Camargo, 2020).

Camargo (2020) explained that it is therefore worth to note the studies carried out by Aránzazu Gonzáles Canga et.al (2010), demonstrated remarkable safety using doses of Ivermectin, higher than those suggested. Doses of 1000ug / kg for 3 days, for example, showed no adverse effects, even with additional doses of 200ug / Kg there were no problems, highlighting that the drug's metabolism is widely distributed, mainly in hepatic peroxisomes.

With his own study (Case Report), Camargo assures that he has evidence that Ivermectin represents, so far, the most powerful and effective "coronicidal" agent that exists for the rapid treatment and attack of the pathogen. Therefore he maintains that the application deserves to be massive in the face of the threat of the pandemic, since its use is simple to apply and far superior, in terms of safety and toxicological profile, compared to other drugs.

Broward County (South Florida) Ivermectin Protocol

Rajter et al (2020), at the Broward Health Medical Center, followed on a retrospective cohort study of consecutive patients hospitalized at four Broward Health hospitals in South Florida with confirmed SARS-CoV-2. Two hundred and eighty patients with confirmed SARS-CoV-2 infection (mean age 59.6 years [standard deviation 17.9], 45.4% female), of whom 173 were treated with ivermectin and 107 given usual care, were reviewed. Twenty seven identified patients were not reviewed due to multiple

admissions, lack of confirmed COVID results during hospitalization, under 18 years of age, pregnancy, or incarceration. Exposure: Patients were categorized into two treatment groups based on whether they received at least one oral dose of Ivermectin at 200 micrograms/kilogram at any time during the hospitalization in addition to those receiving usual clinical care. Treatment decisions were at the discretion of the treating physicians. Rajter et al (2020) concluded that Ivermectin was associated with lower mortality during treatment of COVID-19, especially in patients who required higher inspired oxygen or ventilatory support. The authors suggested these findings should be further evaluated with randomized controlled trials.

Mass Administration of Ivermectin

Mass Drug Administration (MDA) consisting of administering, at regular intervals, a full antimalarial treatment to the whole population, in this case several African Countries that follow MDA of ivermectin, will be analyzed for the COVID-19 impact.

Dihydroartemisinin (also known as dihydroqinghaosu, artenimol or DHA) is a drug used to treat malaria. Dihydroartemisinin is the active metabolite of all artemisinin compounds (artemisinin, artesunate, artemether, etc.) and is also available as a drug, in itself. It is a semi-synthetic derivative of artemisinin and is widely used as an intermediate in the preparation of other artemisinin-derived antimalarial drugs (Woo, 1998). It is sold commercially in combination with piperaquine and has been shown to be equivalent to artemether/lumefantrine (Arinaitwe et al, 2009). African countries such as Senegal, Burkina Faso, Liberia, Tanzania, etc. have achieved excellent results with ivermectin and dihydroartemisinin-piperaquine (Foy et al. 2019; Romani et al. 2019; Alout, Haoues. 2014).

The WHO (2016) reported that in 2014 alone, more than 260 million people were treated with ivermectin for onchocerciasis/ Lymphatic Filariasis (LF). Due to its success, the LF programme has been downscaled in 11 countries. The global demand for ivermectin is expected to grow due to additional indication for scabies and new evidence that a single dose of Ivermectindiethylcarbamazine (DEC)-albendazole can accelerate LF elimination. Ivermectin is currently donated to countries' NTD programmes through the Mectizan® donation programme. The main delivery strategy is through community volunteers annually, semiannually, or quarterly.

The Madagascar Protocol

The U.S. President's Malaria Initiative (PMI)—led by the U.S. Agency for International Development (USAID) and implemented together with the U.S. Centers for Disease Control and Prevention (CDC), delivers cost-effective, lifesaving malaria interventions alongside catalytic technical and operational assistance to support Madagascar to end malaria (MOP, 2020).

This Malaria Operational Plan (MOP) outlines planned PMI activities in Madagascar for Fiscal Year 2020. Developed in consultation with the National Malaria Control Program (NMCP) and key stakeholders, proposed activities reflect national and PMI strategies, draw on best-available data, and align with the country's context and health system. Proposed PMI investments support and build on those made by the Government of Madagascar, as well as other donors and partners (MOP, 2020).

PMI organizes its activities and planning levels around the activities, in line with the national malaria strategy. One of the activities has to do with Diagnosis and Drug Based Prevention. The treatment for malaria includes Artemisinin Based Combination Therapies (ACT) plus primaquine (MOP, 2020). ACTs are the mainstay of recommended treatment for P. falciparum malaria (WHO, 2020). Artemisinin is isolated from the plant Artemisia annua, sweet wormwood, a herb employed in Chinese traditional medicine to treat malaria. According to MOP (2020) the first-line treatment is artesunate-amodiaquine (ASAQ), and second-line treatment is artemether-lumefantrine (AL). According to the country's case management guidelines, P. vivax malaria should be treated with ASAQ followed by a 14-day course of primaquine. Severe malaria cases are treated with injectable artesunate followed by ACT. Rectal artesunate was recently introduced at the community level for pre-referral treatment of children less than five years of age (CU5) with severe disease. It is important to keep in mind that artesunate and artemether are semisynthetic derivatives of artemisinin, an antimalarial drug.

The Malaria Operational Plan operates both nationally and in support of the National Malaria Control Program, planning policies and malaria commodities, with direct program support in 10 regions of the country, covering a population of approximately 12,500,000 (MOP, 2020). This is what is known as Mass Drug Administration (MDA).

The President of Madagascar, Andry Rajoelina, officially launched a natural medicine he believes can prevent and cure people suffering from COVID-19. Developed by the Malagasy Institute of Applied

Research and branded COVID Organics, President Rajoelina presented the remedy to the press. It contains Artemisia, a plant cultivated and exported on the Big Island to fight against malaria. “All trials and tests have been conducted and its effectiveness in reducing and eliminating symptoms has been proven for the treatment of patients with COVID-19 in Madagascar,” the president said. Humanity is living an ongoing dramatic story where its survival is at risk. We do not have the luxury of turning our backs to a healing plant that already has shown excellent medicinal properties for thousands of years (Abreu, 2020).

A Final Analysis

Clear age trends in coronavirus deaths have been reported since early in the pandemic. Research teams looking at the presence of antibodies against SARS-CoV-2 in people in the general population in Spain, England, Italy, and Geneva in Switzerland, have now quantified that risk. It gives us a much sharper perspective when asking what the impact might be on a certain population that have a certain demographic (Mallapaty, 2020).

For every 1,000 people infected with the coronavirus who are under the age of 50, almost none will die. For people in their fifties and early sixties, about 5 out of 1000 will die - more men than women. The risk climbs steeply as the years accrue. For every 1,000 people in their mid-seventies or older who are infected, around 116 will die. These are the stark statistics obtained by some of the first detailed studies into the mortality risk for COVID-19 (Mallapaty, 2020).

The countries compared in this research are:

The United States of America (USA), Mexico, Canada, Francia, Madagascar, and in addition the World global data, was taken as a reference. The data used was from the period of April 2020 to Nov 02, 2020.

Cambaza (2020) explained that COVID-19 is not spreading quickly in Sub-Saharan regions, possibly due to a combination of several factors, one being the predominance of younger populations. In the present analysis, the age factor has no impact on the calculations.

In the study, Madagascar showed the highest percentage of younger population, while Canada showed the lowest percentage. For this reason, to minimize the impact of the age factor in the comparative

analysis of this study, the age factor was standardized in the countries analyzed, to a population of 25 years and over (Table 1).

Table 1. Madagascar Protocol. Hypothetical Scenario. Data from April 2020 to Nov 02, 2020
Population ≥ 25 years

Country	Population ≥ 25 years	# Deaths April–Oct 29, 2020	Death/Million April-Oct 29, 2020	Hypothesized Deaths	Lives that could have been saved
U.S.A	68.26% 224,750,463	221,978	987	4,944	217,033
FRANCE	69.72% 46,966,430	29,151	620	1,033	28,117
MEXICO	56.04% 70,587,538	91,693	1,299	1,552	90,140
CANADA	72.94% 26,172,082	9,922	379	575	9,346
MADAGASCAR	40.22% 10,329,948	244	23	-	-
WORLD	58.93% 4,422,005,946	1,131,105	255	97,284.00	1,033,821

Weekly Updated Calculations by Dr. Jose Luis Abreu. Spenta University Mexico. www.spentamexico.org
Based on data from The World Health Organization

In table 1, based on data from WHO and the World Factbook (2020), Madagar´s Deaths per Million (23) is compared with the World (255), the USA (987), Mexico (1,299), Canada (379), France (620) and the World (255). The calculated differences that significantly surpass Madagascar in number of deaths per million are:

- USA: 987-23= +964
- Mexico: 1,299-23= +1,276
- Canada: 379-23= +356
- France: 620-23= +597
- World: 255-23= +232

Departing from these results of the analysis, and taking as a reference the Madagascar factor, it can be hypothesized about lives that could have been saved:

- USA: 217,033
- Mexico: 90,140

- Canada: 9,346
- France: 28,117
- World: 1,033,821

Dr. Marcel Razanamparany (2020), President of the National Academy of Medicine of Madagascar, expressed that in a race against time to find a cure for COVID-19, Madagascar began early therapies associated with treatments derived from traditional knowledge with emphasis on the use of medicinal plants. With Madagascar's rich biodiversity and the central role of its traditional practitioners, the decision was made to promote traditional medicine (The African Report, 2020).

It was announced by Razanamparany (2020) that under the presidential coordination of Madagascar for the use of Artemisia annua against the coronavirus, the Malagasy Institute of Applied Research (IMRA) and the National Pharmacology Research Centre joined forces to conduct studies and set up a research protocol on this plant already known for its virtues against malaria. This led to the development of Covid-Organics, an improved traditional remedy made up of artemisia. Abundant on Malagasy soil, the artemisia annua has already been the subject of more than twenty studies in Madagascar where it was introduced in 1975 by Professor Albert Rakoto Ratsimamanga to fight against malaria.

The research protocol enabled the IMRA team, which has been working on this plant for a long time, to verify its good results in reducing and eliminating coronavirus symptoms. This is another discovery for this research centre, which has some fifty remedies to its credit, developed by combining traditional and modern medicine, including the antidiabetic drug Madeglucyl and the cough supressant Madetoxin (Razanamparany, 2020).

This medical and pharmaceutical research and training centre, IMRA, was founded in 1957 thanks to the financial benefits of a healing drug, Madecassol, which its founders Albert and Suzanne Rakoto Ratsimamanga derived from the centella asiatica plant. The centre is nationally and internationally renowned and has been granted the status of regional research centre by the African Union (Razanamparany, 2020).

IMRA is located in Antananarivo and composed of a team of about a hundred people, including some thirty researchers and technicians, its research focuses on phytochemistry, parasitic and cellular

pharmacology, experimental diabetology, pharmacodynamics, toxicology and the analytical chemistry of essential oils. It was recognized as being of public utility by the Government Council on 2 October 2012 (Razanamparany, 2020).

IMRA has aimed to adopt an approach to scientific research that integrates health care, biodiversity conservation, and production. In the course of its work, IMRA has advocated practices that protect the environment, respect local culture, and empower local populations to share in the economic benefits of bioprospecting. IMRA's relationship to traditional Malagasy healing has been important to the organization's achievements to date (Puri, Masum and Heys, 2010).

The development of Covid-Organics has been explained by Razanamparany (2020). It is a perfect illustration of the credo of Professor Albert Rakoto Ratsimamanga, whose research focused on the combination of traditional and modern medicine. Regarded as the pioneer of science in Madagascar, this researcher, who was at the origin of some 350 scientific studies, declared: "We must move forward at our own pace, we must above all have confidence in ourselves and in the therapeutic virtues of nature. For nature and man are one."

The data presented in this research paper exemplify how Madagascar has turned into a profound, ongoing global research study, providing scientific evidence in real time within populated communities. Its significance, relative to sectorized conventional clinical trials needs to be recognized.

It is time to acknowledge Madagascar for their insightful contribution to the scientific world and humanity.

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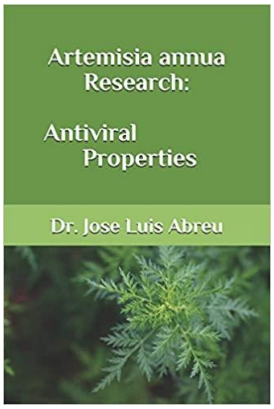
INVITATION

The author would like to kindly invite you to visit the following sites:

Research on the Madagascar Protocol and Coronavirus. Educational Research Center

HIBBERD HEALTH Dr Jennifer Hibberd



Book on Artemisia annua

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