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SARS Cov-2 Structure, biology, immunology and clinical course: Exploring the value of traditional medicine in limiting COVID-19 individual risk and disease outcomes

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Since the onset of COVID-19 in early 2020, various approaches have been adopted worldwide by various state health authorities containing the ravaging pandemic. Tanzania adopted additional approach based on Tanzanian Traditional Medicines. This review aimed to explore the suitability of this local approach based on evaluation of the virus biology, pathogenesis and immunology in relation to the traditional medicines, nutritional immunology, steaming practice and nutritional contents of medicinal plants and potential impact of their combinations. Data related to COVID-19, dietary therapy and herbal medicine were systematically searched and gathered in scholarly materials. The search strategy included all terms that contain key words in relation to COVID-19 and treatment using traditional approach. Over 188 published articles on COVID-19 virus that included the virus biology, pathogenesis and immunology in relation to the traditional medicines, nutritional immunology, steaming practice, medicinal plants and nutritional contents of medicinal plants were obtained after individual manual screening. Given the relatively lower cases of the pandemic in Africa and the approach that Tanzania and some other African countries have used, it is undeniable that other factors than host-pathogen interaction determine the severity of the infection by the SARS-CoV-2 to necessitate multiple approaches to contain the disease. The authors conclude that traditional medicines potentially contain variable compounds with immunological, antiviral activity and nutritional value which, combined with steaming practice, can limit the virus impact while providing relief or protection to patients against the disease and be the key local interface remedy in keeping the COVID-19 low in Tanzania and other African countries to contain the pandemic.

Key words: Nutrition therapy, traditional medicine, COVID-19, nutritional immunology, steam therapy.

INTRODUCTION

On 31 December 2019, the World Health Organization (WHO) China Country Office was informed by the Chinese authorities of a new type of corona virus identified as novel corona virus (nCoV) in Wuhan, Hubei Province that has been responsible for the now pandemic corona virus disease (COVID-19) that has resulted in
nearly 183.6 million confirmed cases and claiming over 3.98 million (2.17%) deaths worldwide. The virus was identified through active case finding and retrospective review of all suspected cases and the virus that was isolated on 7th January 2020, has now spread all over the world raising a health crisis globally. The first confirmed case of COVID-19 was reported in Tanzania on 16th March, 2020 in Arusha region. The number of cases kept increasing and after five weeks since the first case was reported there were at least five confirmed cases of COVID-19 in all Tanzania regions. COVID-19, like other viral diseases has no cure though can potentially be restrained via application of relevant vaccine, which is in infancy development for public use globally. Various pharmaceutical firms are busy worldwide trying to find suitable vaccine to this new disease by corona virus containment. In the due period, various nations via their health authorities have either decided to follow a WHO approach for united fight against the disease but some countries have taken different approaches which they feel fits their settings. Wearing N95 surgical masks and cloth masks which have been available locally and in different versions has been proposed to be a universal preventive respiratory hygienic measure to reduce human to human transmission via nasal or oral droplets. These, together with observance to social distancing, lockdown, hand washing hygiene and working from home (self-isolation) have largely and promisingly reduced man-man transmission (CDC, 2020; WHO, 2020a) despite that in some settings, these have not got endorsement by communities, COVID-19 comes in mild, moderate and severe forms with 80% of the forms being asymptomatic, thus a good idea is to ensure that in an area where the virus is circulating, all proposed hygienic measures (CDC, 2020; WHO, 2020a, 2020b) are observed.

One control strategy that has been difficult to practice in most developing countries has been ‘the lockdown’ due to lifestyle and nature of activities of citizens in these countries. As a result, some countries have opted to not go on lockdown but observe proposed WHO measures but restricting some groups such as students from primary school to universities or college closing. Whether preventive or therapeutic, some African countries including Tanzania have been forced to advocate the use of various traditional medicines and foods for their people as a remedy for the striking pandemic. Tanzanian government softened the pandemic’s threat and encouraged the use of local and homemade herbal remedies such as a mixture of ginger and lemon tea, steam therapy, national wide prayer as additional strategies to prevent COVID-19 infection (Kwayu, 2020). There are reasons for most developing countries to resort to cheap and readily available traditional medicines believably effective in producing relief or preventing people from succumbing to this fearsome pandemic infection. The foremost reason that emerged earlier in the development of the disease is lack of trust to available and scanty vaccines. Others may include, but not limited to the costs of the vaccines and other modern remedies e.g. diagnosis and hospital machine oxygen supply, stigma, poor knowledge of the disease in some societies due to local beliefs and attitudes, government leaders advocacy on traditional medicine and absence of reliable remedy to this new pandemic. Experience in Tanzania has also recovered individuals disinterest to social distancing and use of masks, the practices which are potentially important in reducing chances of transmission from infected to healthy ones. These all have forced people to rely on the use of traditional medicine and various foods to combat this fearsome pandemic. This review aimed to explore the suitability of this local approach based on evaluation of the virus biology, pathogenesis and immunology in relation to the traditional medicines, nutritional immunology, steaming practice and nutritional contents of medicinal plants and potential impact of their combinations. The review therefore, addresses in depth, of various issues including SARS Cov-2, the etiology of COVID-19, its structure and biology, the clinical course of Covid-19, immunology and host factors affecting individual risk and outcomes. The idea is to create a base for traditional medicine researchers to work on scientific basis that can be useful as evidence for medicinal plants use as alternative to modern remedies to combat COVID-19. This may be necessary to the device choice of medicine and approach for different individuals depending on different stages of the disease.

**METHOD FOR LITERATURE SEARCH**

A grey literature search of PubMed, Google and Google Scholar retrieved over 188 published articles on COVID-19 virus that included the virus biology, pathogenesis and immunology in relation to the traditional medicines, nutritional immunology, steaming practice, medicinal plants and nutritional contents of medicinal plants as well as assessing their potential impact singly or in their combinations. All unpublished work that had relevant information but useful to the article was not referred in this review. We limited our search to English articles or English translated articles where necessary. The idea was to obtain information on various traditional approaches believed to be used in various local settings as preventive to COVID-19 given the absence of formal medical approach and vaccines. The search terms included but not limited to “COVID-19 and Etiology; Coronavirus and etiology, COVID-19

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and Biology; Coronavirus and Biology; COVID-19 and Pathogenesis; COVID-19 and Immunology; Nutrition and Immunity to Infections; Vitamins and Immunity to Infections; COVID-19 and Traditional Medicines; Steaming and Respiratory Infections; Steaming and COVID-19; Medicinal Plants and contents; Medicinal Plants and Nutrition Contents; COVID-19 and Medicinal Plants; Medicinal Plants and Antiviral Activities; COVID-19 and Dietary Therapy; Herbal Medicines and Immunomodulatory; and Herbal Medicines and Antiviral Activities”. Since the disease is new, we did not limit search terms to specific country or region in order to get the broader perspective from various communities worldwide, the information we thought was most relevant to our write up.

RESULTS AND DISCUSSION
This paper examines various scenarios underlying the potential role of the approach in limiting the COVID-19 infection and its impact. To achieve this, this part of the study was on the virus structure, its biology, pathogenesis and immunology of the disease. Then, present data related to COVID-19, dietary therapy and herbal medicine. The perspective is an opinion regarding the use of foods and herbs as a prevention and complementary therapy against COVID-19.

COVID-19
SARS Cov-2 structure and biology
Novel human coronavirus (SARS-CoV-2) has a probable animal origin that has emerged in less than two decades (Decaro and Lorusso, 2020). Severe Acute Respiratory Syndrome Coronavirus 2 (SARS Cov-2) is a member of a group of coronaviruses which belongs to Coronaviridae family (Gorbalenya et al., 2020). Viruses in the Coronaviridae family are distributed in four Genera (α,β,δ,y,) which have been identified so far, with the α and β group being associated with Human coronavirus (Li et al, 2020). SARS Cov-2 is an enveloped virus, with a positive sense, single-stranded RNA, genome. The virus has a 29.9 Kb genome size, and it belongs to the Betacoronavirus (β) Genus. Two other RNA viruses belong to this genus, and are responsible for the previous Important Flu epidemics in the last two decades. The viruses are Middle East Respiratory Syndrome Coronavirus (MERS Cov) and Severe Acute Respiratory Syndrome (SARS Cov) Coronavirus. In animals, the novel corona virus strains, different antigenic, biologic and pathogenetic features, pathogenicity with variations in tissue tropism and host range are well known (Decaro and Lorusso, 2020).

SARS Cov-2 Genome organization
Like other Coronaviruses, SARS Cov-2 genome consists of at least 10 Open Reading Frames (ORFs). The first ORF occupies 2/3 of the whole genome and codes for 16 non-structural proteins which forms the viral replicase-transcriptase complex. The complex facilitates viral replication and transcription. The remaining 1/3 of the genome codes for the viral structural proteins including Spike (S), Envelope (E) Membrane (M), Nucleocapsid (N) and other accessory proteins which are not associated with viral replication (Pachetti et al, 2020).

The order of genes in the SARS Cov-2 genome 5’ to 3’ was studied and predicted as follows: replicase ORF1ab, Spike (S), ORF 3a, Envelope (E), Membrane (M), ORF 6a, ORF7a, ORF7b, ORF8, Nucleocapsid (N) and ORF10. This makes a complete genome of 29903 nucleotides, 29.9 Kb. The size of each gene is well elaborated in Figure 1. Among the predicted ORF 10, had no comparative proteins in the NCBI repository, but proposed that could potentially be useful in distinguishing infections rather than the commonly used PCR methods (Khailany et al., 2020).

SARS Cov-2 Replication
Coronavirus uses its Spike protein (S) to facilitate entry into the host cell. The Spike glycoprotein uses the Angiotensin Converting Enzyme 2 (ACE 2) as its receptor for attachment with the host cell (Li et al., 2020). For the virus to enter the cell, the S protein needs to be proteolytically cleaved into two domains, the S1 domain which facilitate the receptor binding of the virus to the host cell, and the S2 domain which facilitates host cell membrane fusion (Lu et al., 2020).

After the internalization of the virus into the cell, the viral RNA is released into the cytoplasm and translated where ORF 1a/b is translated to two poly proteins forming the non-structural proteins (nsp (CDC,2021; WHO, 2020a; WHO, 2020b; Kwayu 2020; Decaro and Lorusso 2020; Gorbalenya et al., 2020; Li et al., 2020; Pachetti et al., 2020; Pachetti et al., 2020; Khailany et al., 2020; Lu et al., 2020; Cui et al., 2019; de Wit et al., 2016; Koh and sng, 2010; Millet and Whittaker, 2014; Perlman and Netland, 2009; WHO, 2020a)), and the remaining ORFs are translated to structural proteins such as the Spike, Envelope, Nucleocapsid and Membrane proteins. The non-structural proteins form the viral replicase transcriptase complex responsible for rearranging membranes from the Rough Endoplasmic Reticulum to form double membrane vesicles where viral replication and transcription takes place (Li et al., 2020). The newly formed envelope glycoproteins are inserted in the endoplasmic reticulum and Golgi apparatus of the host cell. The nucleocapsid protein combines with the viral genome to make the nucleocapsid. The viral particles then assemble into the Endoplasmic reticulum-Golgi intermediate compartment. Lastly, a vesicle containing the viruses fuses with the plasma membrane and released (Li et al., 2020).
Pathogenesis (and mode of infection)


Transmission of COVID-19

The origin of SARS-Cov-2 and how it has spread to humans is not clearly understood and until recently no definitive reservoir or intermediate host has been identified. However, studies on genomic analysis of SARS-Cov found in bats in China was shown to be more than 95% identical to the SARS-Cov-2 isolated in humans responsible for the Covid-19 pandemic, suggesting a possible link between humans and other mammals (Lu et al., 2020; Zhou et al., 2020a). The most common route of transmission of Covid-19 is person to person transmission usually through direct contact or droplets from an infected person through coughing or sneezing, thus the chances of transmission is reduced with physical distancing. So far there has been no evidence suggestive of vertical transmission of Covid-19 from mother to the unborn child. Studies have shown that the entry of the SARS-Cov-2 into the nasal mucosal cells is facilitated by the envelope spike protein S that binds to the host cell angiotensin-converting enzyme 2(ACE2) receptor; (Jaimes et al., 2020; Wan et al., 2020a). The infection is established by the binding the SARS-Cov-2 virus with the ACE2 receptors located on the ciliated epithelial cells in the nose and throat mucosal surfaces (Li et al., 2003; Zhou et al., 2020). The binding of SARS-Cov-2 is much higher compared to other SARS-Cov viruses (Wrapp et al., 2020). To facilitate the entry of the virus, the spike protein is cleaved by the respiratory tract cell membrane protein fusin exposing the viral receptor binding domain which locks into the ACE2 receptors. This SARS-Cov-2 receptor specific binding domain is absent in the bat viruses and is what makes SARS-Cov-2 able to infect humans (Zhang et al, 2020). Studies have shown that unlike the SARS-Cov-2 which infects both the upper and lower respiratory tract, its predecessors; SARS-Cov and MERS-Cov poorly infect the upper respiratory tract (Cyranski, 2020).

The clinical course of COVID-19

Based on the accumulated experiences from China and the increased number of patients from Europe, United States, South America and recently in Africa, the clinical course of Covid-19 is between 14-21 days and can be classified into three main categories namely; asymptomatic, mild to moderate and severe disease (Zhou et al., 2020a; Berlin et al., 2020; Gralinski et al., 2020; Gralinski et al., 2020).

Asymptomatic COVID-19

In the period where different communities have experienced coronavirus infection, the virus has been found to affect different people in different ways. Most infected people develop mild to moderate illness and recover without hospitalization. There is a possibility that vast majority of SARS-Cov-2 infected individuals may remain asymptomatic. During this period, most of the patients exhibit no symptoms, but an RT-PCR test of nasal swab for the virus will be positive, and the individuals may be able to spread the infection unnoticed. At this stage COVID-19 infected patients can only be identified if screening programme has been adopted in the given health settings.
Mild to moderate COVID-19 (upper respiratory tract infection)

The duration from exposure to the virus until the Covid-19 symptoms develops varies. On an average, this period ranges from 4 to 5 days, and has been shown that over 90% of symptomatic patients develop symptoms within the first 11 days (Lauer et al., 2020). This is the period when the SARS-CoV-2 virus spreads in the ciliated cells in the nose and throat, and is the time when the host innate immune system mounts a robust challenge to fight against the virus. As the disease progresses, individuals initially start manifesting mild to moderate respiratory tract infection characterized by flu-like symptoms including; fever, severe headache, cough, running nose, malaise, myalgia, and anosmia (Lauer et al., 2020; Gandhi et al., 2020; Giacomelli et al., 2020). Laboratory findings may include lymphopenia, elevated C reactive protein, D dimer and lactate dehydrogenase. With just supportive treatment, the over 80% of these patients recover at home (Gandhi et al., 2020; Wallace et al., February–April 2020).

Severe COVID-19 - acute respiratory distress syndrome

Studies have shown that less than 20% of covid-19 infected individuals develop lung disease and few end up with severe disease resulting in deaths among 1-2% of all cases (Berlin et al., 2020). The commonest symptom of severe covid-19 is difficulty in breathing (dyspnea) which is associated with hypoxaemia (Wang et al., 2020; Zhou et al., 2020b). Much as SARS-CoV-2 is highly infectious compared to its predecessors SARS-CoV-1 and MERS-Cov, however, most of the infected individuals seem not to progress to implicate the lower respiratory tract. If it reaches the lungs, the SARS-CoV-2 virus infiltrates into the alveoli, where studies both in vitro as well as in vivo have shown the type II alveoli cells to be the primarily targets (Mossel et al., 2008; Weinheimer et al., 2012). The destruction of the alveoli cells and the associated apoptosis and destruction of blood vessels in the lungs leads to accumulation of fluids hindering oxygen exchange in the lungs resulting into dyspnoea and hypoxaemia. The host’s immune response to the severe inflammation in the lungs may succeed in some individuals, however, to some particularly the elderly or individuals with underlying diseases including; hypertension, obesity, diabetes, coronary heart diseases and asthma the damage and associated inflammatory response that is similar in all SARS will result in adverse health outcomes including death (Grasselli et al., 2020; Zhou et al., 2020b). Recent studies have shown that the exceedingly severe/robust immune response referred to as cytokine storm is what gives rise to widespread organ (liver, kidney, heart, brain, spleen etc.) failure and eventually death (Guo et al., 2020; Guo et al., 2020; Huang et al., 2020; The ADTF, 2012). The widespread damage to the lung by Covid-19, and the host’s response try and repair the damage may result in severe fibrosis and scarring, impairing the respiratory function much further (Faccenda et al., 2001; Maruyama et al., 2007; Xu et al., 2020). Thus, individuals with comorbidities and the elderly are at risks because of their inability to mount a robust immune response and tissue repair mechanisms.

Overall, the basis of the lung parenchymal damage and the resulting widespread multi-organ failure which is the commonest cause of death in severe covid-19 is the consequence of uncontrolled host and viral inflammatory responses. In the second year of the pandemic, there is still much to be discerned on the exact mechanisms of Covid-19 pathogenesis at the moment that will get clearer with time.

COVID-19 immunology

Coronaviruses (CoV) that affect humans can be divided into two groups namely (i) Low pathogenic that infect the upper respiratory tract and may cause mild to cold-like respiratory illness. (ii) Highly pathogenic such as severe acute respiratory syndrome CoV (SARS-CoV) and Middle East respiratory syndrome CoV (MERS-CoV) mostly infect lower airways and may cause deadly pneumonia. The severe pneumonia due to pathogenic human CoVs is accompanied by increased virus replication, massive inflammatory cell infiltration, and increased pro-inflammatory cytokine/chemokine responses which leads to acute lung injury (ALI) and also acute respiratory distress syndrome (ARDS) (Channappanavar and Perlman, 2017).

In comparison to infections with SARS-CoV and MERS-CoV, COVID-19 has milder symptoms, even though some key pathogen-associated with clinical characteristics are similar. There is currently limited information on host factors affecting individual outcomes of COVID-19. Therefore, most scientists infer the existing knowledge about the pathophysiology of SARS and MERS to better understand COVID-19 infection (Felsenstein et al., 2020).

Hematopoietic cells such as dendritic cells (DCs), monocyte, macrophages and other peripheral blood mononuclear cells (PBMCs)-derived cells are thought to be affected in SARS-CoV infection. Infection of DCs induce low level expression of antiviral cytokines IFN-αβ, moderate up-regulation of pro-inflammatory cytokines TNF and IL-6, and a substantial up-regulation of inflammatory chemokines CCL3, CCL5, CCL2, and CXCL10 (Cheung et al., 2005; Law et al., 2005). Likewise, infection of macrophages shows delayed but increased levels of IFN and other pro-inflammatory cytokines (Law et al., 2005). Furthermore, SARS-CoV-infected airway epithelial cells (AECs) also generate large amounts of
chemokines such as CCL3, CCL5, CCL2, and CXCL10. The deferred and overly produced cytokines and chemokines are thought to induce a dysregulated innate immune response to SARS-CoV infection.

Type I interferon (T1IFN) expression is needed for the host response and clearance of viral infections (Addi et al., 2008). This expression and downstream signals control cell responses and reprogram cells into an "anti-viral state", which later promotes control of infection and pathogen clearance (Lazear et al., 2019). Firstly, immune cells detect viral infection by identifying the virus derived pathogen associated molecular patterns (PAMPs) like viral RNA. The PAMPs bind and activate pattern recognition receptors (PRRs) on immune cells and lead to immune cell activation. Endosomal RNA PRRs, such as Toll-like receptors (TLR-3) and 7 and cytoplasmic RNA sensors namely retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5) are recognized and detected by viruses such as SARS-CoV, SARS-CoV2 and MERS-CoV (Figure 2).

Normally, activation of TLR3/7 leads to nuclear translocation of the transcription factors NFκB and IRF3, whereas RIG-1/MDA5 activation results in activation of IRF3. Consequently, this trigger elevated T1IFN (through IRF3) expression and other innate pro-inflammatory cytokines (IL-1, IL-6, TNF-α through NFκB) (de Wit et al., 2016; Prompetchara et al., 2020). Auto-amplification does occur whereby; T1IFN and other innate pro-inflammatory cytokines promote their own expression. T1IFN triggers the IFN-α receptor complex (IFNAR) which leads to the phosphorylation/activation of STAT family transcription factors 1 and 2 whereas IL-1, IL-6, and TNF receptor activation feeds into pro-inflammatory cytokine expression though the transcription factor NFκB (Figure 2) (Alunno et al., 2019; de Wit et al., 2016; Lazear et al., 2019). Pathogen clearance and recovery is as a result of activation and priming of innate and adaptive immune responses.

In some patients of SARS-CoV, MERS-CoV and likely SARS-CoV2, the virus escapes the immune system recognition through suppression of the above mechanisms, a phenomenon which is linked with more severe disease and poorer outcomes (Figure 2; red symbols) (Channappanavar and Perlman, 2017; Kindler et al., 2016; Lu et al., 2011). Studies have shown SARS-CoV to change ubiquitination and breakdown of RNA sensors (RIG-1 and MDA5). It works by inhibiting activation of mitochondrial antiviral-signaling protein (MAVS) which are crucial for the activation and nuclear translocation of IRF3 in response to cytoplasmic RNA sensor activation. Additionally, SARS-CoV, and possibly SARS-CoV2 prevent the TNF receptor-associated factors (TRAF) 3 and 6 which are key for the induction of IRF-3/7 in response to TLR3/7 and or RIG-1 and MDA-5 ligation as well as NFκB signaling pathways (Kindler et al., 2016). Finally, these novel coronaviruses can counteract T1IFN signaling by preventing phosphorylation of STAT family transcription factor (de Wit et al., 2016). Adding together, the suppression of innate immune mechanisms in infected epithelial cells and to some level, infected monocytes/macrophages permit novel coronaviruses to multiply without triggering the innate anti-viral response machinery of these cells.

During virus infections, cytokines and chemokines have thought to play a key role in immunity and immunopathology. The first line of defence against viral infections is a quick and well-coordinated innate immune response; however dysregulated and excess immune responses may lead to immunopathology (Channappanavar et al., 2016; Davidson, et al., 2015; Shaw et al., 2013). Data from patients with severe disease have suggested a function of hyper-inflammatory responses in hCoV pathogenesis.

Data from SARS patients with severe disease revealed high serum levels of pro-inflammatory cytokines (IFN-γ, IL-1, IL-6, IL-12, and TGFβ) and chemokines (CCL2, CXCL10, CXCL9, and IL-8) compared to individuals with uncomplicated SARS (Chien et al., 2006; Wang et al., 2005; Wong et al., 2004a; Zhang et al., 2004). On the contrary, SARS patients with severe disease had very low levels of the anti-inflammatory cytokine, IL-10 (Chien et al., 2006). Additionally, SARS patients with severe disease showed elevated levels of IFN (IFN-α and IFN-γ) and IFN-stimulated genes (ISGs) (CXCL10 and CCL-2) compared to healthy controls or individuals with mild-moderate disease (Cameron et al., 2008; Cameron et al., 2007; Huang et al., 2005; Theron et al., 2005). These were the first results to suggest a possible role for IFNs and ISGs in the immunopathogenesis of SARS in humans. Therefore, findings from these studies have highlighted the important role in SARS pathogenesis from the dysregulation and/or exaggeration of cytokine and chemokine responses by SARS-CoV-infected airway epithelial cells (AECs), DCs, and macrophages.

In contrast to SARS-CoV infection which terminally infect monocyte-macrophages, DCs, and T cells. MERS-CoV replicates in both naïve and activated human monocyte-macrophages and DCs, only activated T cells support MERS-CoV replication. MERS-CoV infection of THP-1 cells, a monocyte cell line, and human peripheral blood monocyte-derived macrophages and dendritic cells induced delayed but increased levels of pro-inflammatory cytokines and chemokines such as CCL-2, CCL-3, CCL-5, IL-2, and IL-8. Nevertheless, induction of IFN-α/β by monocyte-macrophages and DCs was not significant except for plasmacytoid dendritic cells, which produced large amounts of IFNs upon MERS-CoV infection. Studies have shown that individuals with severe MERS have increased levels of serum pro-inflammatory cytokines (IL-6 and IFN-α) and chemokines (IL-8, CXCL10, and CCL5) compared to those with mild to moderate disease (Kim et al., 2016; Min et al., 2016). There is a correlation between high serum cytokine and chemokine levels in MERS patients and elevated neutrophil and
Figure 2. Immune evasion strategies of SARS-CoV2: A) SARS-CoV2 infects airway epithelial cells through interactions with the trans-membrane enzyme ACE2 (a). While RNA viruses usually activate TLR3 and/or 7 in endosomes (b) and cytosolic RNA sensors RIG-I and MDA-5 (c), SARS-CoV2 effectively suppresses the activation of TNF receptor-associated factors (TRAF) 3 and 6, thereby limiting activation of the transcription factors NFκB and IRF3 and 7, thereby suppressing early pro-inflammatory responses through type I interferons (IFN) and pro-inflammatory effector cytokines IL-1, IL-6 and TNF-α (red symbols). Furthermore, novel CoVs inhibit the activation of STAT transcription factors (d) in response to type I IFN receptor activation, which further limits antiviral response mechanisms. Altogether, this prohibits virus containment through activation of anti-viral programs and the recruitment of immune cells. B) Tissue monocytes/macrophages express ACE2 to a significantly lower extent, making infection through this route less likely (a). However, immune complexes consisting of ineffective antibodies against e.g. seasonal CoVs and virus particles may be taken up by macrophages through Fcγ receptors resulting in their infection (b). In a process referred to as antibody directed enhancement (ADE), virions inhibit type I IFN signalling in infected macrophages while allowing pro-inflammatory IL-1, IL-6 and TNF-α expression, which may contribute to hyperinflammation and cytokine storm syndrome (c,d). Inhibited type 1 IFN signalling suppresses anti-viral programs, while increased IL-1, IL-6 and TNF-α expression auto-amplifies itself through positive feedback loops (f). (Source: (Felsenstein et al., 2020)).

Monocyte numbers in lungs and in the peripheral blood suggestive of a possible vital role for these cells in lung pathology.

**Immune response in people with severe coronavirus disease (COVID-19)**

The critical conditions of COVID-19 disease will start to appear two (2) weeks after the onset of the infection. The common features includes; 1) decreased levels of lymphocytes especially the natural killer (NK) cells in peripheral blood, 2) extremely high inflammatory parameters, including C reactive protein (CRP) and pro-inflammatory cytokines (IL-6, TNFα, IL-8, etc.), 3) the majority of infiltrated immune cells in lung lesion are monocytes and macrophages, but minimal lymphocytes infiltration and, 4) mimicry of vasculitis, hypercoagulability
and multiple organs damage.

Most patients with severe COVID-19 experience of inflammatory cytokine storm (CS), an excessive and uncontrolled release of pro-inflammatory cytokines. The clinical presentation includes systemic inflammation, multiple organ failure and high inflammatory characteristics. In SARS and MERS, together with rapid virus replication, large number of inflammatory cell infiltration and CS lead to acute lung injury, acute respiratory distress syndrome (ARDS) and eventually death (Zhu et al., 2020).

Lymphocytopenia is one prominent indication of severe COVID-19. Although these patients tend to have lymphocytopenia, and their lymphocytes are activated. A study investigated lymphocyte subsets and cytokines in 123 patients of mild and severe cases, lymphocytopenia was observed in all patients and the percentage of CD8+ T cell reduction were 28.4% and 61.9% respectively and the NK cell reduction were 34.3% and 47.6% respectively (Wan et al., 2020).

Other presentations that have been observed in most severe COVID-19 patients include very high level of erythrocyte sedimentation rate (ESR), CRP, and high level of IL-6, TNFα, IL-1β, IL-8, IL2R and these were associated with ARDS, hypercoagulation and disseminated intravascular coagulation (DIC), which showed thrombosis, thrombocytopenia and gangrene of extremities (W. Zhang et al., 2020). It is postulated that CS aggravates lung damage and also leads to other fatal complications. Recognizing that COVID-19 illness displayed three grades, (Siddiqi and Mehra, 2020) proposed a 3 stage classification model of increasing severity which corresponded with different clinical outcomes and response to therapy.

A small percentage of COVID-19 patients would enter into the most severe stage of illness, or the third phase which appear as an extra-pulmonary systemic hyper inflammation syndrome. At this stage, markers of this syndrome seem to be highly elevated. Henceforth, in order to reduce the death rate due to COVID-19, one needs to find therapeutic mechanisms of blocking the CS and know when to initiate anti-inflammation therapy.

Several studies have revealed data that suggest hyper-inflammation that is linked to more severe disease. Studies from Wuhan have linked cytopenia and significant increase in inflammatory parameters with severe disease and adverse outcomes (Felsenstein et al., 2020). One of the studies that involved 99 patients, reported neutropenia, lymphopenia and elevated systemic inflammatory proteins such as IL-6 and CRP as common symptoms in COVID-19 disease (Chen et al., 2020). Another study with 41 individuals linked severe disease terminating in ICU admission and eventually death, with neutrophilia and lymphopenia (Wu et al., 2020). The last study reported significant lymphopenia, leukopenia, thrombopenia, anaemia, hypofibrinogenemia and hypo-albuminemia in 85 patients who died from COVID-19 (Du et al., 2020). These findings are similar to what is observed in lethal cases of MERS and SARS whereby, there are elevated levels of neutrophils and monocytes/macrophages in the airways (Perlman and Dandekar, 2005; Zumla et al., 2015). Other studies (Mahallawi et al., 2018; Wong et al., 2004a, Wong et al., 2004b), done in a different group have shown findings that suggest uncontrolled inflammation which eventually contributes to poor outcomes.

**Host factors affecting individual risk and outcomes**

Age is one of the factors that are associated with poor outcome in Covid-19 infection. Children are believed to contract the disease, but do not develop severe symptoms or complications. The reason is that, more than 75% of children do get exposed to seasonal coronaviruses before the age of 5 years and seroconverts. As the age goes up, the antibody titres decrease mostly for those over 60 years. As a result, this may reduce immune response to SARS-CoV2 in the elderly as cross-reactivity between anti-seasonal coronavirus and anti-SARS antibodies exists, but also add up to increased inflammation and complications.

Through a process called antibody-dependent enhancement (ADE), antibody-bound virions can enter susceptible cells, such as macrophages through Fcγ receptor. Furthermore, in elderly patients with immense recall antibody production and a history of exposure to seasonal coronaviruses but waning titres, can result in immune complex deposition and promote inflammation and damage, including immune complex vasculitis (Gao et al., 2015). Live vaccinations such as measles or BCG may be associated with disease mechanisms. Protection of vaccines is beyond their target antigen through the induction of innate mechanisms, which are termed non-specific heterologous effects (Felsenstein et al., 2020).

ACE2 acts as a transmembrane cellular receptor to SARS-CoV and SARS-CoV2 to establish infection. This receptor is expressed in almost all organs in the body; however, it is highly expressed on surfactant producing type 2 alveolar cells, on ciliated and goblet cells in the airways (Hedrich, 2020). Variation in ACE2 expression patterns affect disease susceptibility between tissues such as respiratory epithelia vs immune cells, but possibly also in individuals between (men vs women, children vs adults) thereby determining disease progression and outcomes. Recent studies have suggested that ACE2 expression is mostly highest in children and young women, the expression decreasing with age, and lowered in patients with chronic diseases such as diabetes and hypertension (J. Chen et al., 2020; Chen et al., 2020). This correlates inversely with risk for severe disease and unfavourable outcomes.

Apart from facilitating the viral entry into cells, ACE2 also functions in regulating infection and inflammation. It
is part of the ACE2/angiotensin-MAS system as it prevents the pro-inflammatory effects of the angiotensin-1-7. It catalyses angiotensin-2 processing into angiotensin-1-7, which prevents vasoconstriction, modulates leukocyte migration, cytokine expression, and fibrogenic pathways (Simões et al., 2013). By so doing, ACE2 subsidises the limiting tissue inflammation while offering repair mechanisms. Thus, high expression of ACE2 may be of beneficial as SARS-CoV2 virus particles may compete with angiotensin-2 for cell surface binding sites and cellular uptake. Therefore, moderately higher ACE2 expression levels may explain why children and young adults, especially young women, are relatively protected from COVID19 and associated complications. SARS-CoV2 may effectively defeat early T1IFN responses, which contributes to uncontrolled virus replication which results in delayed and possibly elevated cytokine responses at later stages. Individuals with highest risk to suffer from the disease such as the elderly, patients with diabetes or metabolic syndrome, early and adequate control of virus replication and clearance of pathogens may be changed (Huang et al., 2020; Lu et al., 2020). In comparison, healthy children and young people, may effectually control viral load at early stages of infection and less frequently develop severe disease and life-threatening complications (Felsenstein et al., 2020). Finally, having early antibody production may contribute in integration of viable virus into immune cells and increased viral replication, which may result in immune complex mediated pathology. This may result to pathology in young patients with no obvious risk factors (Jin et al., 2020).

Contribution of traditional medicines and foods in combating COVID-19 pandemic

The use of traditional medicines as a potential remedy for management and treatment of various diseases has been practiced by billions of people both in developing and developed countries for decades. In developing countries including Africa and Asia, especially in the rural areas, traditional medicines are the only easily accessible and affordable alternative for treatments of different ailments (Dash et al., 2017). World Health Organization (WHO) estimates that more than 80% population in Africa and Asia relies on traditional medicine as primary treatments of various diseases ("WHO (2002) WHO Traditional Medicine Strategy 2002-2005, World Health Organisation Geneva. doi: WHO/EDM/TRM/2002.1.").

Medicinal plants

The medicinal importance of plants relies on their chemical compounds which are of many kinds (Lovkova et al., 2001). Countless pharmaceutical drugs have been derived from plants, for example, artemisinin, an antimalarial drug from plants Artemisia annua (Hao et al., 2002), a plant which also contains phytochemical compounds like phenolic (TPC), flavonoid (TFC) that are potential antioxidants (Iqbal et al., 2012). Some of the few common plants have been locally used for the management of various diseases including flu, cough, and malaria (Hilonga et al., 2019). These plants contain important phytochemical compounds (Awuchi, 2019), which make them pharmacologically useful and potential alternative herbal remedies for relieving and treating various medical conditions and infection including treatment of infection caused by SARS-ncov-2. During this pandemic of SARS-ncov-2 these plants have been utilized as an important component of steam inhalation for treatment of SARS-nCov-2 infection. For instances:

**Eucalyptus robusta (Swamp mahogany)**

Eucalyptus robusta contains phytochemicals like quinones, saponins, carbohydrates, tannins, phenols, flavonoids and fat (Brielmann et al., 2006), some of which have potent pharmacological actions against inflammation, diabetes, hepatotoxicity and cancer (Brielmann et al., 2006).

**Cymbopogon citratus (Lemongrass)**

Cymbopogon citratus contains phytochemical compounds like alkaloids, saponins tannins, anthraquinones, steroids, phenols and flavonoids (Asaolu et al., 2009; Gupta et al., 2019) with proven anti-inflammatory and analgesic property (Gbenou et al., 2013).

**Azadirachta indica (Neem)**

Azadirachta indica contains plenty of phytochemicals with antimicrobial, anti-inflammatory and antioxidant properties like Alkaloids, Flavonoids, Saponins (Dash et al., 2017).

**Zingiber officinale Roscoe (Ginger)**

Zingiber officinale is the most common spice and widely used as a medicinal plant for treatment of different diseases that includes nausea, vomiting, treating colds, pulmonary afflications, joint ailments, headaches and orchitis (Abascal and Yarnell, 2009). Ginger rhizome possesses several outstanding bioactive non-volatile phenolic compounds such as gingerols, paradols, shogaols and zingerones (Langner et al., 1998). 6-gingerol is the one of bioactive phenolic phytocompound found in the fresh ginger rhizome which has activities to several diseases associated with inflammation and viral disease (Rathinavel et al., 2020). The presence of 6-

ginger bioactive phenolic phytochemical makes ginger to possess antiviral activities against human respiratory syncytial virus (HRSV) (Chang et al., 2013). Fresh ginger rhizomes could inhibit viral spreading by inhibiting viral attachment and penetration to minimize viral production and possibly stimulating IFN-β secretion that contributed to the inhibition of viral replication (Chang et al., 2013). A study on antiviral activity of Ginger against human respiratory syncytial virus (HRSV) has already indicated that, fresh ginger is effective against HRSV-induced plaque formation on the airway epithelium by blocking viral attachment and internalization (Chang et al., 2013). Further studies have revealed that phytocompound 6-gingerol from ginger acts as a promising drug to treat COVID-19 with anti-viral efficiency against SARS CoV-2 showing the highest binding affinity and interaction with multiple targets of COVID-19 including Viral proteases, RNA binding protein and Spike protein (Rathinavel et al., 2020).

Apart from anti-viral activities, ginger can as well treat other symptoms of COVID-19 including nausea and shortness of breath (De and De, 2020). Dried ginger have also been shown to effectively reduce nausea and vomiting with 1000mg of dried ginger reducing nausea and vomiting in pregnant woman (Ozgoli et al., 2009) and with fewer side-effects (Pongrojapaw et al., 2007). One tablespoon of ginger syrup can reduce vomiting in a dose given four times per day for two weeks in an attempt to control vomiting and nausea (Keating and Chez, 2002). As such, some studies have reported fresh ginger to be an effective medication to treat nausea and vomiting that are combined with common colds, chest pain and abdomen, retention of phlegm and shortness of breath (Hsu, 1986).

**Camellia sinensis (Tea plant)**

*Camellia sinensis* (L.) Kuntze (Tea plant) is a species that belong to the plant family Theaceae, whose leaves and leaf buds are widely used to make tea, including black tea, white tea and green tea (Namita et al., 2012). Green tea is made from unfermented leaves and reportedly has the highest concentration of powerful antioxidants called polyphenols (Thasleema, 2013). Polyphenols contained in teas are classified as catechins (Musial et al., 2020). Green tea has six primary catechin compounds which includes; catechin, gallaogatechin, epicatechin, epigallocatechin, epicatechin gallate and apigallocatechin gallate (EGCG) that is in high quantity (Chopade et al., 2008).

In the study of active compounds found in plants that have potential to inhibit the proliferation of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), showed that epigallocatechin gallate had better binding free energies with \( \text{M}^{\text{pro}} \) and S protein of SARS-CoV-2. This compound has a potential anti-viral phytochemical that may inhibit the replication of the virus (Tallei et al., 2020) and is able to inhibit the proteolytic activity of SARS-CoV 3CL\(^{\text{pro}}\) (Nguyen et al., 2012). Black tea has three phenolic compounds Tannic acid, 3-isotheaflavin-3-gallate, and theaflavin-3.3′-digallate that has inhibitory effects on SARS-CoV 3CLpro, with \( I_{50} \) values of 3, 7, and 9.5 \( \mu \)M, respectively (Chen et al., 2005).

**Artemisia annua (sweet wormwood)**

Artemisia annua is a medicinal plant used for the treatment of different diseases, dry leaf powder has been reported for the treatment of diarrhea and whole plant decoction used for treatment of malaria, cough and cold (Sadiq et al., 2014). *Artemisia annua* has bioactive compound called artemisinin that have been commercialized as antimalarial drugs and it is most promising natural products that are important candidates accounting for the antiviral effects (Haq et al., 2020). Also *Artemisia annua* has sterols that show virus inhibitory potential (Haq et al., 2020). *In vitro* studies have reported whole plant ethanolic extract from *Artemisia annua* to potentially effective against SARS-CoV infectious diseases (Li et al., 2005).

**Steaming practice and its medicinal value (concepts underlying its value)**

Steam inhalation practice is one of the major treatments for respiratory complications and is recommended for dealing with common cold, flu, bronchitis, sinusitis, asthma, and allergies (Hoffmann, 2017). Steam can be useful whether inhaled in vaporized or moist therapy (Block et al., 2000). Dry air passages are moistened, and mucus is loosened and eliminated easier by coughing or by blowing the nose. The moist air also alleviates difficulty breathing, throat irritation and inflammation (Ray, 2017). Application of steam relaxes muscles and is used to treat arthritis, rheumatism, and sore muscles, chest cold and flu, vasodilation. The advantages of steaming comprise of detoxification, loosening tense muscles and assisting relaxation, enhancing metabolic rate and digestion activity, cell hydrating. In addition, it also boosts the immune system by its efficient functioning and also improves internal organs functioning by stimulating blood supply (Nagaich, 2016).

Amid trials of various drugs and therapies for treating Covid-19 patients, doctors at the Seven Hills Hospital have conducted a study using steam. According to study, steam has a temperature of about 70 to 80 degrees Celsius which is well above the instability temperature of SARS-CoV-2 virus. Moreover, it is known that viruses get killed at 56 to 60 degrees Celsius. Study revealed a drastic drop in the symptoms of Covid-19 virus after the patients were administered with steam. Moreover, there was no further transmission observed in patients taking steam (“Coronavirus in Mumbai: Study shows positive
Research on rhinoviruses has revealed that these viruses grow optimally around 33°C, but their growth is impaired around 37°C (Macknin et al., 1990). A study by Tyrrell (1988) showed some evidence that increases the nasal mucosal temperature from 33 to 37°C along with humidification would limit viral replication and decrease nasal stuffiness. Studies by Yerushalmi and Lwoff (1980) showed dramatic symptomatic improvement in actively treated patients. (Ophir and Eldad, 1987) reported that inhalation of hot water results in alleviation of cold symptoms and increased nasal patency in a significantly higher percentage of patients in the actively treated group than in the placebo treated group. (Tyrrell et al., 1989) also showed that nasal hyperthermia could improve the course of the common cold and give immediate relief of symptoms.

Steam inhalation practice sometimes combines herbs and essential oils with hot water to create therapeutic steam. Essential oil steams are a good way to deliver therapeutic properties directly to the airways for relieving congestion, aches, and general discomfort of colds, flu, and other virus (Bharkatiya et al, 2008). For example, eucalyptol essential oils, the main component in Eucalyptus, have antimicrobial properties and may fight off the bacteria that cause illnesses. Eucalyptol may also help to reduce inflammation, relieve pain, and ease muscle tension that can result from a cold or flu (“EDQM - European Directorate for the Quality of Medicines,” https://www.edqm.eu/ (accessed Aug. 11, 2020).”). The antimicrobial and antiviral activity of essential oils has been confirmed by numerous studies (Swamy et al., 2016). The use of essential oils vapors can increase their application against airborne bacteria and viruses. The anti-influenza virus activity of some essential oil vapours, such as that of Citrus bergamia (bergamot), Eucalyptus globulus (eucalyptus), Pelargonium graveolens (geranium), Cinnamomum zeylanicum leaf oil (cinnamon), and Cymbopogon flexuosus (lemongrass), has been reported. Their inhibitory mechanism is based on the inactivation of the principal external proteins of the influenza virus (Vimalanathan and Hudson, 2014). Oregano essential oil contains a high level of a potent compound called carvacrol. Authors of a 2014 study found that carvacrol is an effective antimicrobial agent that fights off many types of germ and sinuses issues (Schuetz, 2020). A 2015 animal study suggested that lavender essential oil may have analgesic, or pain-relieving effects, and that it also reduces inflammation (Da Silva et al., 2015). When menthol, a property of peppermint essential oil, is inhaled, it creates a cooling sensation that can soothe or numb a scratchy throat. A 2013 study suggests that when a person uses peppermint oil, it can help to relax the bronchial muscles; this explains why the oil can ease breathing in people with coughs (Semenya and Maroey, 2018). Tea tree essential oil can inhibit the growth of the bacteria that cause sinus infections and respiratory issues (Council of Europe; European Pharmacopoeia Commission (2007).

**The contribution of foods and nutrition and their antiviral activities against infection**

It is known that Good nutrition is very important before, during and after an infection. Infections take a toll on the body especially when these cause fever, the body needs extra energy and nutrients. Therefore, maintaining a healthy diet is very important during the COVID-19 pandemic. While no foods or dietary supplements can prevent COVID-19 infection, maintaining a healthy diet is an important part of supporting a strong immune system. In this review, the aim was to report records on the antiviral activity of a particular diet and herbal medicine on influenza virus, SARS-CoV-1, and SARS-CoV-2. This will promote the use of dietary therapy and herbal medicine as interface complementary COVID-19 prevention therapies, given the current absence of effective drug and/or vaccine against COVID-19/SARS-CoV-2. It is also possible that, nutrient rich diets and herbal medicine, may be key complementary to modern medicines or vaccines even if will be already found. The following foods and micro-nutrients have the strongest evidence for immune support and many have been shown to have general anti-viral properties: Vitamin C, Vitamin D, Zinc, Vitamin A, Vitamin E, Selenium and Plant Phytonutrients (from plant-based foods) may have antioxidant, anti-inflammatory and anti-viral effects. Whether these are specifically effective for COVID-19 is yet to be elucidated, however, these are generally protective and can potentially help to support individuals' overall health.

**Quercetin, immunity and COVID-19**

Quercetin is a plant pigment (flavonoid) found in many plants and foods, and is said to have unique biological properties that may improve mental, physical performance as well as minimizing risks to infections (Davis et al., 2009; Li et al., 2016). The pigment is found in vegetables but also in red wine, onions, green tea and a variety of fruits including apples and berries (Davis et al., 2009). Due to its medicinal value, people use quercetin as a medicine in some parts of the world including USA. Different laboratory and animal studies have indicated that quercetin may inhibit a wide variety of viruses, including a coronavirus (SARS-CoV) related to COVID-19 (Colunga et al., 2020). In a study where mice were injected with influenza, quercetin was shown to...
restore diminished concentrations of many antioxidants in the lungs including catalase, reduced glutathione, and superoxide dismutase. It was then concluded that quercetin taken in conjunction with viral infection may support antioxidant capacity and protect lung tissues (Kumar et al., 2005). However, human studies looking at quercetin and viral load in humans are limited.

**Vitamin A, immunity and COVID-19**

According to available information, Vitamin A supports the health of mucosal tissues and barrier function (Villamor and Fawzi, 2005). Retinoic acid, which is a metabolite of vitamin A, also helps regulate the immune system via the microbiome (Cassani et al., 2012). COVID-19 appears to impact mucosal tissues throughout the body; therefore vitamin A can potentially be a supportive nutrient to complement the protective mucosal barrier function. Beef liver, cod liver oil, sweet potatoes, carrots, black-eyed peas, spinach, broccoli and supplementation are the good sources of vitamin A.

**Vitamin C, immunity and COVID-19**

Available evidence shows that vitamin C is among the important nutrients for immune health, especially for white blood cells to fight infections. It also enhances iron absorption, and adequate iron can help protect against vulnerability to infection. Vitamin C is thought to be effective against COVID-19; however, clinical studies are required to confirm this. Vitamin C includes foods such as guava, kiwi, bell peppers, strawberries, oranges, papaya, broccoli, tomato, kale, grapefruit, persimmon, spinach and pineapple. Recent information indicate that mega-doses of oral vitamin C have not been shown to protect against coronavirus, although trials are currently underway testing the ability of intravenous vitamin C to protect against the effect of a cytokine storm (Peng, 2020). Overall, vitamin C is supportive of the immune system, especially in those who are deficient (Hemilä and Louhiala, 2013).

**Vitamin D, immunity and COVID-19**

There are a number of reviews of the role of vitamin D and its metabolites in immunity and in host susceptibility to infection. Available evidence shows that vitamin D decreased the risk of COVID-19 outbreak in winter, which is a time when 25-hydroxyvitamin D (25(OH)D) level is low. Thus, vitamin D intake may reduce the risk of influenza and COVID-19 infections and related deaths (Grant et al., 2020). In a systematic review assessing the overall effect of vitamin D supplementation on the risk of acute respiratory tract infection, Vitamin D supplementation reduced the risk of acute respiratory tract infection among all participants. The most benefit was seen in those who were very vitamin D deficient and those not receiving mega-doses (Grant et al., 2020). Thus, optimizing vitamin D status is a likely safe and helpful measure for protection against respiratory infections in general (Grant et al., 2020). Vitamin D is not found in sufficient amounts in most foods, so exposure to sunlight is important and possibly supplementation if 25-hydroxy vitamin D levels are suboptimal.

**Vitamin E, immunity and COVID-19**

Vitamin E while, not specifically an anti-viral nutrient, vitamin E is one of the most efficient antioxidants and plays an important role in lung and liver protection. As a fat-soluble nutrient, it can accumulate in lipid membranes and react quickly with free radicals that trigger nuclear factors that produce cytokines (Closa and Folch-Puy, 2004). Deficiencies can alter immune responses and contribute to increased viral load (Beck, 2007). Vitamin E foods include sunflower seeds, almonds, avocados, spinach, butternut squash, kiwi, broccoli, olive oil, trout and shrimp.

**Selenium, immunity and COVID-19**

Selenium is a potent antioxidant and a cofactor of glutathione peroxidase, an important antioxidant enzyme. A deficiency of selenium can alter the immune response and increase the pathogenicity of a virus (Beck, 2007). Food sources include tuna, shellfish, eggs, sunflower seeds, and shitake mushrooms.

**Zinc, immunity and COVID-19**

Zinc may improve the chance of avoiding respiratory tract infections in the elderly and those who are zinc deficient (Ananda S Prasad et al., 2007). Food sources include Oysters, beef, crab, and lobster, and to a lesser extent chicken, cheese, kidney beans, garbanzo beans, cashews, and almonds.

**Potential impact of combinations (steaming vs consumption), traditional medicine vs nutritious foods**

The longstanding use of dietary therapy and herbal medicine to prevent and treat diseases cannot be overemphasized, as several herbs exhibit antiviral activity. Using dietary therapy and herbal medicine to prevent SARS-CoV-2 infections could be a complementary COVID-19 therapy while drugs and
vaccines development is underway. In general, nutrition is not a cure for COVID-19 but healthy patterns of eating optimize the function of the immune system, improve immune-metabolism, and are a modifiable contributor to the development of chronic disease that is highly associated with COVID-19 deaths. Nutrition may have a positive impact on COVID-19 as it may be a way to support people at higher risk for the disease that is older people and people with pre-existing conditions such as Diet Related Non-Communicable Diseases (DRNCDs). Many foods and herbs are known to display antiviral and immunomodulatory activities. However, these observations must be verified through scientific or clinical studies. Rice bran, wheat bran, Lawsonia alba (hina), Echinacea purpurea (eastern purple coneflower), Plumbago zeylanica (Ceylon leadwort), and Cissampelos pareira Linn (velvetleaf) also exhibit immunomodulatory properties by stimulating phagocytosis. Eucalyptus essential oil is reported to improve the innate cell-mediated immune response that can be used as an immunoregulatory agent against infectious diseases (Serafino et al., 2008) (Sadlon and Lamson, 2010). Collectively, using these immunomodulatory foods and herbs could enhance the immune system and protect the body against COVID-19.

What is important is to work hard and find out which foods or traditional medicinal plants are rich in potentially infection protective nutrients or compounds and include them in their diets and medicines to fit in their local setting (Fawzi and Stampfer, 2003). It is therefore necessary that clinical trials should be considered for some of the Tanzanian dietary therapy and herbal medicine claimed to manage COVID-19. Home treatment of contacts and mild COVID-19 cases may become commonplace necessitating some evidence-based measures in addition to the management guidelines currently in place. This role could be played by dietary therapy and herbal medicine to boost immunity or prevent infection if explored carefully to exploit their potential role.

In nutritional immunology, it is important to understand how best it can exploit the dietary contents, their nutritional value and nutritional factors that singly or collectively influence the immune responses to various infections. Among nutrition impact on immune response includes regulation of health and disease outcomes. Under normal situations, the impact of nutrition on body defense cannot easily be recognized until when the detrimental effect of malnutrition on the immune system becomes conspicuous. Thus uncovering nutritional component with immunological value is important in the mitigation of infectious diseases and is very critical if timely and efficiently respond to various types of infections. Thus, investing the understanding on the mechanisms by which nutrients protects against infections and particularly, key nutrients that have been systematically studied and their pathway directly or indirectly to support the healing process is necessary.

Existing evidence on micronutrients indicate positive role in conferring protection against not only metabolic diseases but also a major role in boosting body defense against infections (Maggi et al., 2007). Vitamin D deficiency or insufficiency for example, has been ascribed with modulation of inflammatory responses and that may be responsible for inter-individual variations in pulmonary inflammation and viral pathogenicity including COVID-19 (Carter et al., 2020; Pereira-Santos et al., 2015). The vitamin, particularly its biologically active form, is 1,25-dihydroxyvitamin D/calcitriol and has been implicated in various inflammatory, infectious, and pulmonary diseases relieved through supplementation (Charan et al., 2012; Martinez et al., 2017). However, in a community with micronutrient deficiency, it is not uncommon multinutrient rather than single nutrient deficiency is the most prevalent. Thus diet rich in diverse micronutrients will ensure a broad nutrient profile to pertinently alleviate vulnerability to acute and chronic disease (Carter et al., 2020). With SARS-CoV-2 (COVID-19), it has been proposed that Vitamin D prophylaxis, without over-dosing, may contribute to reducing the severity of illness, particularly in settings where severe Vitamin D deficiency is frequent (Jiménez-Sousa et al., 2018; Panarese and Shahini, 2020). Immunologically, Vitamin D is said to be potentially induce development modulation of its stimulatory actions as well as influencing of cell-mediated immunity thus strengthening immune response to infections (Bock et al., 2011; Crenier et al., 2016; Hewison, 2012; Wintergerst et al., 2007). With change in lifestyle including dietary factors and physical activity which are usually modifiable (Carter et al., 2020), the severity of COVID-19 can be greatly reduced and the disease be contained (Brainman, 2020). COVID-19 comes with cold and flu-like symptoms; therefore, vitamins B, C and D, as well as zinc may be helpful in boosting immune response to the infection and help fighting the illness in the same way as it occurs with other colds and flus (Jayawardena et al., 2020). Through its antioxidant effects, vitamin C can help reduce inflammation thus reducing severe symptom of COVID-19 due to lung inflammation. A Clinical Senior Lecturer at University of Sheffield (Gariballa, 2005) further stresses vitamin and mineral supplements to prevent infections in particularly older people with evidence of vitamin and mineral deficiencies. This emphasizes the need for sufficient supply of nutrient rich supplements to reduce the severe impact of COVID-19 which has been found to much affect particularly the old age group. The reduction in the severity of the disease could be due to improved immune system following supplementation singly or as multinutrient supplements of vitamins A, C, and E, and zinc and selenium (Lesourd, 1997; Wintergerst et al., 2006; Wintergerst et al., 2007).

Studies on African nutrient poor stunting children, have shown positive effects of micronutrients, particularly zinc and magnesium on growth, malaria incidences and
giardia infection (Veenemans et al., 2011a; Veenemans et al., 2011b; Veenemans et al., 2012) and their role mainly seemed to be immunological by altering both type I and type II cytokine immune responses (Mbugi et al., 2010a; 2010b) with potential that they also influence antibody responses (Mbugi et al., in preparation). Zinc has been ascribed to prevent and reduce symptoms of various respiratory infections including shorten the length of colds, relief from nasal congestion, nasal drainage, sore throat and cough (Martinez-Estevez et al., 2016). The effect of zinc extents to immunological role whereby it leads to help in production and activation of T-cells (t-lymphocytes) thus triggers the body to respond to infections (Rondanelli et al., 2018). The effect of zinc on immune response ranges from cellular natural immunity to adaptive immune response where supplementation has been found to increase cellular components of innate immunity such as phagocytes cells namely, macrophages and neutrophils, natural killer cell activity, and generation of oxidative burst (Maggini et al., 2007). Zinc supplementation have been ascribed to immunobalancing of inert cytokines such as IL-1, IL-2, IFN-gamma, IL-6, TNF-alpha, (Calder and Kew, 2002; Isbaniah et al., 2011; Pinna et al., 2002; Ananda et al., 2008; Wieringa et al, 2010) as well as blocking of Intracellular Adhesion Molecule (ICAM-1) (Martinez-Estevez et al., 2016). The secretion of IL-2 receptors is also reduced in zinc-deficient individuals (Pinna et al., 2002). With zinc supplementation, adaptive immune response enhanced through proper antigen presentation via MHC-II (Hojo and Fukada, 2016), T-cell differentiation (Fortes et al., 1998; Isbaniah et al., 2011; Sazawal et al., 1997), enhanced T-Cell functions and receptor expressions (Barnett et al., 2016; Isbaniah et al., 2011). As well as enhanced early B-cell development and mature B cells maintenance (Hojo and Fukada, 2016). All these evidence can be important in uncovering scientific basis underlying the effect of the use of local and home remedies in alleviating the impact of COVID-19 in patients as well as prevention from getting infected. The question could be, can steam therapy contribute significantly in providing nutrients to the patient?

Conclusion

Since emergence of the COVID-19, it was predicted that Africa would suffer a massive loss of life due to the pandemic; however, the number of COVID-19 cases has been relatively low across the continent compared to other continents. Tanzania, have peculiarly not reported new cases since the 509 cases, 21 deaths and 183 recoveries back in April, 2020. The disease seems to have cycles of waves of infections peaking from January to June, as per observations when moving to year 2 since the start of the pandemic. Some speculations show several factors to potentially be responsible for the reported low cases in Africa, including the extensive experience with infectious diseases and the young median age of their populations (Musa et al., 2021). Although this idea can be supported with the reported evolutionary structural resemblance of the SARS-CoV-2 with other similar viruses (Mittal et al., 2020), there is no evidence to support potential existence of cross-reactive immunity against SARS-CoV-2 (Maani et al., 2020) and pre-existing immunity role is still questionable (Doshi, 2020) and potentially immunopathogenic (Beretta et al., 2020). Given the relatively lower cases of the pandemic in Africa and the approach that Tanzania and some other African countries have used, it is undeniable that other factors than host-pathogen interaction determine the severity of the infection by the SARS-CoV-2.

In this review, the authors explored the potential contribution of protective immunity, nutrition and herbal medicines in protecting and treating patients infected with the SARS-CoV-2, the etiological agent for COVID-19. The review has every potential to enable people hypothesize that, pre-existing immunity due various exposures to infections, nutrition and nutrient contents of traditional medicines, complemented by steaming are key in keeping the COVID-19 low in Tanzania and other African countries advocating for traditional medicines to contain the pandemic. Recent publication on steaming inhalations (la Marca et al., 2021), has further endorsed that the procedure based on cycles of steam inhalation may be beneficial in halting SARS-CoV-2 virus infection in the upper airway mucosae during the initial stages of infection while preventing further spread. This is crucial achievement, as an interface remedy when efforts for developing relevant drug or vaccine are underway. During infection, the SARS-CoV-2 is thought to induce dysregulated innate immune response that may be due to deferred and overly produced cytokines and chemokines. In this particular case the balance in these early responses can be brought about by micronutrients like zinc and magnesium that are contained in our regular diets (Mbugi et al., 2010a; 2010b) and possibly in orally taken traditional medicines further emphasizing on the value of medicinal plants. This might include but not limited to vitamins such as Vitamin A, C, D, E and minerals such as selenium in addition to aforementioned nutrients which might have antiviral activities (Gariballa, 2005; Jayawardena et al., 2020; Jiménez-Sousa et al., 2018; Lesourd, 1997; Panarese and Shahini, 2020; Wintergerst et al., 2006, 2007).

Current literature carries strong evidence in support of dietary therapy and herbal medicine as potential effective antivirals against SARS-CoV-2 and preventive agents against COVID-19. For the future research, there are 4 potential areas for the application of dietary therapy and herbal medicine against COVID-19: (1) using foods and herbs as diet or supplement to prevent infection and strengthen immunity; (2) use as an antiviral agent by
coating on masks; (3) use as an air-disinfectant (essential oil) to stop aerosol transmission; and (4) use as a surface sanitizing agent to provide a disinfected environment. Surgical masks are good at preventing virus spread into the air and transmission to humans (Greenhalgh et al., 2020; Leung et al., 2020). However, after mask removal, the virus remains on the mask and is probably re-aerosolized, increasing the risk of human infection and re-infection. Mask coating with an antiviral compound could be advantageous, but disinfectant toxicity (residue effects) to humans must be evaluated before it is considered for endorsement. Majority of restaurants and some households use cleaning detergents for surface sanitization; however, their safety and disinfection efficiency need further consideration. Natural antiviral extracts from herbs could be added to cleaning detergents to increase their anti-SARS-CoV-2 activity with increased potential for safety. From this review the authors can further hypothesize that traditional medicines could contain variable compounds with immunological, antiviral activity and nutritional value which is combined with steaming practice, and can limit the virus impact while providing relief or protection to patients against the disease.

CONFLICT OF INTERESTS

The authors have not declared any conflicts of interests.

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