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Harnessing nutritional immunity and advanced diagnostics for COVID-19 prevention

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ABSTRACT

The ongoing worldwide health crisis caused by the COVID-19 pandemic, which began in Wuhan, China, has led to infections across the globe. Although many vaccines are available, a definitive cure has yet to be found. This study examines methods to lessen the impact of the disease, focusing on preventive actions and strengthening the immune system through diets rich in vitamins and nutrients. Our investigation also considers non-traditional methods, particularly the vital role of early detection in controlling the spread of COVID-19. Accurate diagnostic techniques are essential in this effort. Surprisingly, there is a lack of comprehensive studies on the complex interactions between various vitamins, trace metals, and immunity in relation to COVID-19. Addressing this gap, our review carefully analyzes how diets enriched with vitamin D can boost immunity. Additionally, we explore worldwide challenges that impede the progress of effective and quick diagnostic methods. Our goal is to provide a thorough understanding of the current situation regarding immunity, diagnostic procedures, and treatment approaches for COVID-19. This review not only covers various diagnostic methods for SARS-CoVs but also assesses the effectiveness of different vaccines against COVID-19. Through detailed analysis, we contribute to the ongoing discussion on fighting COVID-19, providing important information for researchers, healthcare workers, and policymakers.

1. Introduction

In December 2019, pneumonia, cough, and severe throat infection of some unknown cause were reported in Wuhan, China, with clinical symptoms resembling viral pneumonia. The novel coronavirus-induced pneumonia with dry cough in humans was named coronavirus disease 2019 (COVID-19) by the WHO on February 11, 2020. Since then, the infection has become a major healthcare threat, with devastating effects for the elderly and people with pre-conditions such as diabetes, hypertension, cancer, and breathing problems (Zhou et al., 2020a).

Two decades earlier, there was an outbreak of severe acute respiratory syndrome (SARS) caused by coronaviruses (SARSr-CoVs) (Li et al., 2005; Ge et al., 2013; Hu et al., 2017). Some studies at that time showed that SARSr-CoV were mainly found in bats and that they could be a source of futuristic diseases (Fan et al., 2019; Huang et al., 2020a). Recently discovered SARS-CoV-2 is responsible for the COVID-19 pandemic and is the seventh member belonging to enveloped, positive-stranded RNA viruses that have the potential to cause viral infection in humans (Zhu et al., 2020).

SARS-CoV-2, upon inhalation, most likely binds to epithelial cells in the nasal cavity and immediately starts replicating (initial infection 1-2 days). Human ACE2 (angiotensin I-converting enzyme-2) and TMPRSS2 (transmembrane protease serine 2) are the main receptors for both SARS-CoV2 and SARS-CoV and the gate for the virus to enter the host cell (Hoffmann et al., 2020; Wan et al., 2020). Studies demonstrate that SARS-CoV initially infects the ciliated cells in the conducting airways (Qian et al., 2013).

In the second step (a few days later), after infecting the nasal cavity, the SARS-CoV2 starts migrating towards the respiratory tract. This triggers the innate immune system to respond against the viral infection. At this stage, the infection of COVID-19 is clinically manifested, and the level of cytokine could be a source of prediction for subsequent clinical courses (Tang et al., 2005). The

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epithelial cells, after infection with the virus, alert the body cells to initiate the formation of beta and lambda interferons (Hancock et al., 2018). Interferons are a type of cytokine that is part of the family of secretory proteins. They alert immune cells to the presence of infectious pathogens in the body. CXCL10 is a gene that responds to interferons; it activates when viruses like SARS-CoV and influenza infect alveolar type II cells. CXCL10 is also identified as a marker of disease in cases of SARS and influenza (Tang et al., 2005; Qian et al., 2013; DeDiego et al., 2014).

In the third step, SARS-CoV2 approaches the gas exchange unit of the lungs with the propagation of infection to alveolar type II cells. Moreover, SARS-CoV2 and influenza specifically infect alveolar type II as compared to alveolar type I (Mossel et al., 2008; Weinheimer et al., 2012). Alveolar type II cells are crucial for producing pulmonary surfactants, substances that help prevent the collapse of alveolar cells. However, when SARS-CoV-2 infects these cells, it releases a large number of viral particles. This ongoing infection leads to the collapse and death (apoptosis) of alveolar type II cells (Qian et al., 2013). It is reported that release of SARS-CoV2 particles into alveolar type II cells leads to diffuse alveolar damage with fibrin-rich hyaline membranes and multinucleated giant cells (Hui and Zumla, 2019; Xu et al., 2020). Recovery is based on well-established innate immune responses and epithelial cell regeneration. Elderly people are considerably at higher risk because of weak immune systems and loss of the capability to repair epithelial damage. They are also at mucociliary clearance risk, allowing the fast spread of SARS-CoV2 to the exchange unit of the lungs (Whitsett, 2018). People infected with COVID-19 have symptoms like fever, fatigue, myalgia, headache, diarrhea, dry cough, and dyspnea that finally result in acute respiratory distress syndrome (Huang et al., 2020b). While the respiratory system remains a primary target, COVID-19's influence extends well beyond the lungs, affecting the immunological, cardiovascular, neurological, and other vital systems. In this review, we also explored the intricate interplay between SARS-CoV-2 and the human body, shedding light on the extensive effects of COVID-19 on different systems.

1.1. Respiratory system

The emergence of the novel coronavirus SARS-CoV-2 in late 2019 has a dramatic and far-reaching impact on world health, most notably on the human respiratory system (Wang et al., 2020b). COVID-19, the disease caused by this virus, predominantly presents as a respiratory illness with a diverse array of clinical manifestations (Brosnahan et al., 2020). Typical symptoms encompass cough, fever, breathlessness, and fatigue, indicative of the virus's capacity to infect both the upper and lower respiratory tract (Courtney and Bax, 2021). In severe cases, patients may develop the incapacitating illness known as acute respiratory distress syndrome (ARDS), which is characterized by hypoxia, visible pulmonary infiltrates on imaging, and reduced lung compliance (Ball et al., 2022).

SARS-CoV-2 gains entry into host cells by binding to angiotensin-converting enzyme 2 (ACE2) receptors, which are prominently expressed within the respiratory tract. This interaction facilitates viral replication, which results in localized inflammation and tissue damage (Marini and Gattinoni, 2020; Sharifkashani et al., 2020; Jafary et al., 2021). The following immunological reaction to the viral invasion triggers a cytokine storm, resulting in excessive inflammation that can inflict harm on lung tissue and impede respiratory function (Huang et al., 2020a; Jiang et al., 2022). Furthermore, COVID-19 is capable of inducing endothelial dysfunction and the formation of microthrombi in pulmonary blood vessels, exacerbating the impairment of oxygen exchange. A subset of patients, particularly those afflicted with severe disease, may develop pulmonary fibrosis as a consequence of prolonged inflammation, potentially leading to persistent respiratory impairment (Jin et al., 2020; Andrade et al., 2022; Vianello et al., 2022).

A subset of individuals experiences a condition termed "long COVID," characterized by enduring symptoms such as persistent cough, breathlessness, chest discomfort, and fatigue persisting for weeks or even months after the resolution of the acute infection (Vestad et al., 2022). Chronic lung scarring may result in compromised lung function, persistent breathlessness, and diminished exercise capacity. The COVID-19 pandemic has brought to light the profound impact of this virus on the human respiratory system, encompassing not only the acute phase of infection but also the potential for long-term consequences (Vaniprabha et al., 2022; Huerne et al., 2023).

1.2. Cardiovascular system

The global healthcare systems have been significantly strained by the COVID-19 pandemic, unearthing a multitude of effects on various organ systems, notably the cardiovascular system. COVID-19 induced myocardial injury either through direct viral invasion or inflammatory processes, with studies reporting heightened levels of cardiac biomarkers like troponin and creatine kinase-MB among COVID-19 patients, indicative of myocardial damage. In more severe cases, COVID-19 can incite myocarditis, characterized by heart muscle inflammation, potentially leading to heart failure and arrhythmias (Siripanthong et al., 2022; Timpau et al., 2022; Kumar et al., 2022).

SARS-CoV-2 can also induce endothelial dysfunction, resulting in compromised vascular function and pro-thrombotic conditions. This dysfunction significantly elevates the risk of thromboembolic events (Liu-Fei et al., 2023; Stern et al., 2023). Among COVID-19 patients, there is an increased susceptibility to developing venous

thromboembolism and arterial thrombotic events, which can subsequently manifest as strokes, heart attacks, or pulmonary embolisms. Additionally, some COVID-19 patients experience exacerbations of pre-existing hypertension or the onset of new hypertension, along with the observation of arrhythmias such as atrial fibrillation (Tudoran et al., 2022; Re et al., 2022; Krishnakumar et al., 2022).

A group of patients recovering from COVID-19 continues to struggle with persistent symptoms. Cardiovascular signs such as persistent chest pain and palpitations have been described among these symptoms, raising concerns about potential long-term cardiovascular effects. Research has also revealed the likelihood of post-acute sequelae in some COVID-19 survivors, including chronic myocarditis and cardiomyopathies. COVID-19 has a complex effect on the cardiovascular system, covering direct viral impacts, inflammatory processes, endothelial dysfunction, and thrombotic tendencies (Krishnakumar et al., 2022; Elseidy et al., 2022; Santoro et al., 2023).

1.3. Neurological effects

Emerging evidence indicates that COVID-19 can exert neurological consequences such as loss of taste and smell, headaches, dizziness, and more severe outcomes like encephalopathy and strokes (Mohamadi et al., 2022). This virus may potentially infiltrate the central nervous system, resulting in enduring cognitive outcomes. Although primarily acknowledged as a respiratory ailment, mounting research demonstrates the virus's capacity to influence diverse organ systems, including both the central nervous system (CNS) and peripheral nervous system (PNS). Research findings affirmed that SARS-CoV-2 can directly infiltrate the nervous system, facilitated by the virus's spike protein binding to ACE2 receptors present in the CNS and PNS, thereby potentially gaining access to neural tissue. Neuroinvasion may occur via the olfactory bulb or by traversing the blood-brain barrier (BBB), leading to neurotropic effects (Zirpe et al., 2020; Veleri, 2022; Taga and Lauria, 2022; Chen et al., 2022; Tyagi et al., 2023).

Anosmia (loss of smell) and ageusia (loss of taste) are two early and unique neurological symptoms associated with COVID-19. These sensory disruptions frequently represent initial signs of the disease and can persist, detrimentally impacting patients' quality of life. The virus may inflict direct harm on olfactory neurons or influence the olfactory bulb, thus contributing to these sensory impairments (Algahtani et al., 2022; Di Stadio et al., 2022).

Multiple case studies have demonstrated COVID-19-associated encephalitis and meningitis. These inflammatory disorders can develop because of a direct viral infection, an abnormal immunological response, or as a result of the downstream effects of systemic inflammation. These cases highlighted the critical importance of considering neurological consequences when treating COVID-19 patients (Marques et al., 2022).

COVID-19 is associated with an increased risk of cerebrovascular events, including ischemic strokes and intracerebral hemorrhages. The etiology of these complications is believed to encompass a blend of factors, including hypercoagulability, endothelial dysfunction, and inflammation, and can manifest in individuals devoid of traditional stroke risk factors (Garcia-Azorin et al., 2022). It has been linked to an array of neuropsychiatric symptoms, including depression, anxiety, cognitive impairment, and delirium. The specific mechanisms underlying these symptoms are complicated and multifaceted, involving both the direct impact of the virus on the brain and the psychosocial consequences of the pandemic (Sojka et al., 2022).

A significant number of COVID-19 survivors experience chronic neurological symptoms, which might include fatigue, cognitive impairments, and neurological manifestations such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) (AlMuhaissen et al., 2023). COVID-19 can incite a hyperactive immune response, potentially culminating in autoimmune neurological disorders such as Guillain-Barré syndrome (GBS). GBS is characterized by ascending weakness and paralysis and can emerge as a post-infectious complication of COVID-19 (Filosto et al., 2022).

1.4. Immune system dysfunction

COVID-19 can cause immune system dysregulation, resulting in an excessive inflammatory response known as a cytokine storm. This immune reaction can cause organ damage and contribute to serious illness. Regarding the Innate Immune Response, SARS-CoV-2 often infiltrates the body via respiratory mucosa, prompting an immediate innate immune reaction. According to research, the virus can evade early immune defenses mostly by suppressing interferon synthesis. The dysregulation of cytokine responses, frequently referred to as the "cytokine storm," is a defining feature of severe COVID-19 patients (Hanson et al., 2022; Sun et al., 2023). Increased levels of pro-inflammatory cytokines like IL-6 and TNF- may cause tissue damage and organ failure. The virus has also been shown to affect the function of natural killer (NK) cells, which are vital for detecting and eliminating infected cells (Elbadawy et al., 2023; Mohammed et al., 2022).

Concerning the Adaptive Immune Response, studies have unveiled a wide array of immune dysregulation patterns in COVID-19 patients. While some patients mount effective adaptive immune responses, others display delayed or insufficient antibody production. The virus can compromise the function of CD4+ and CD8+ T cells, which are crucial for coordinating the immune response and eradicating infected cells. Persistent immune activation and inflammation can lead to T-cell exhaustion, potentially contributing to long-term

immune dysfunction in certain recovered patients (El Karoui and De Vriese, 2022; Hamedi et al., 2023).

Turning to Memory Immune Responses, research suggests that COVID-19 survivors may develop immunity against reinfection, although the duration and strength of this protection can vary significantly among individuals. The virus's capacity to mutate and generate variants may pose challenges to the immunity's lifetime (Sette and Crotty, 2022). In terms of Autoimmunity and Immune Dysfunction, certain COVID-19 patients demonstrate autoimmune-like symptoms, such as cytokine-mediated tissue damage and the creation of autoantibodies. Concerning Vaccination and Immune Response, COVID-19 vaccinations have proven to be highly effective in activating robust immune responses and reducing disease severity. Vaccine-induced immunity may also provide broader protection against variations, boosting the adaptive immune system (Sette and Crotty, 2022; Takao and Ohira, 2023).

1.5. Long COVID (Post-acute sequelae)

Following the resolution of the acute phase of infection, a significant proportion of patients experience persistent symptoms and consequences, which are now referred to as "Long COVID" or "Post-Acute Sequelae of SARS-CoV-2 infection (PASC)." Long COVID provides a complex clinical environment, creating a diagnostic enigma for healthcare providers. Long COVID symptoms include fatigue, dyspnea, chest discomfort, cognitive impairment (often known as "brain fog"), migraines, palpitations, joint pain, and gastrointestinal issues. These residual symptoms last a long time, with some people suffering a repeated pattern of remission and return. Prolonged symptoms may be caused by viral replication, immunological dysregulation, and post-viral inflammatory reactions (Yong and Liu, 2022; Low et al., 2023). In the context of Long COVID, autoimmunity and the existence of autoantibodies have emerged as critical variables. Autoantibodies that target certain proteins have been discovered to cause autoimmune-like events that may contribute to the persistence of symptoms. Dysfunctional immunological responses, defined by persistent inflammation, have been hypothesized as probable drivers in long-term COVID etiology (Damoiseaux et al., 2022; Rojas et al., 2023).

1.6. Mental health

The pandemic, accompanied by its associated stressors, has exerted a significant toll on mental well-being. Anxiety, depression, and post-traumatic stress disorder (PTSD) have all been linked to issues such as social isolation, uncertainty, and health-related concerns. The pandemic triggered a surge of psychological distress and increased anxiety around the world, owing to fears of infection, an uncertain future, and an onslaught of unpleasant news. The anxiety created by lockdowns and social distancing techniques exacerbated this fear (Penninx et al., 2022; Kauhanen et al., 2023).

Throughout the pandemic, studies have consistently reported an upsurge in depression rates. Lockdowns, job losses, and the disruption of daily routines left many individuals grappling with feelings of isolation and loneliness. The prolonged experience of loneliness has the potential to precipitate depression and exacerbate pre-existing mental health conditions. Healthcare professionals and those directly impacted by the virus, such as survivors and individuals who suffered the loss of loved ones, faced an elevated risk of developing PTSD. The constant exposure to death and suffering exacted a severe toll on their mental health (Penninx et al., 2022; Kauhanen et al., 2023; ElTohamy et al., 2022).

During the pandemic, there was also an alarming increase in substance usage. Isolation, stress, and varied coping techniques all contributed to increasing alcohol and drug intake, a condition with long-term consequences for addiction and mental health. The effects of the pandemic on children and adolescents must not be ignored. School closures disturbed routines, and limited social connections hampered their normal growth and created mental health issues (Kauhanen et al., 2023).

Economic downturns and job losses caused financial stress, further contributing to anxiety and depression. Certain people's access to mental health care was also hampered because of financial constraints. Vulnerable populations, including low-income communities, persons of color, and those with pre-existing mental health disorders, faced a disproportionate share of the weight of these effects. Existing inequities in healthcare and access to resources were exacerbated, increasing mental health inequality. The epidemic stressed healthcare systems, making it difficult for certain people to get mental health assistance (Folayan et al., 2022; Liu et al., 2022).

It is worth noting that not all outcomes of COVID-19 on mental health were negative. Some individuals displayed remarkable resilience and developed effective coping mechanisms. These experiences offer valuable insights into the human capacity for adaptation. In summary, the COVID-19 pandemic has left an indelible and multifaceted mark on human mental health. The psychological toll, ranging from heightened anxiety and depression to more severe conditions like PTSD, has been substantial. Vulnerable populations and children have been disproportionately affected. Tackling the mental health repercussions of the pandemic presented a critical challenge for healthcare systems worldwide.

In general, patients with mild COVID-19 can be treated at home, while COVID-19 patients with alveolar type II cell infection must be monitored carefully and treated based on the availability of resources, as no specific antiviral drugs are available for SARS-CoV2 treatment. For the current COVID-19 pandemic, the human body is totally reliant on a strong and uplifted immune system. The human

immune system has shown enhanced capability to fight viral infections with an adequate intake of nutrients and vitamin supplements (Patel et al., 2019). Some recent studies have also shown that essential trace elements such as Zinc and Selenium have improved the immune system in many viral infections (Ivory et al., 2017; Iovino et al., 2018).

The stability of the human immune system depends on proper nutrition and essential trace elements. A deficiency in any micronutrients can significantly affect the responses of the human immune system (Gombart et al., 2020). Recent reviews support the idea that optimal nutrition can protect against many viral infections, particularly those affecting the lungs (Calder et al., 2020; Wu and Zha, 2020). Current literature indicates that there are no pharmacological treatments available for the prevention and treatment of COVID-19. The role of vitamins and other nutrients, as well as diagnostic methods in reducing the risk of viral infections, is summarized from recent studies.

2. Vitamin's role in immunity

2.1. Role of vitamin D in immunity and protection from viral infections

Vitamin D, a prohormone and fat-soluble vitamin plays a crucial role in the absorption of calcium and phosphorus in the body, thereby preventing bone diseases in humans (Sethuraman et al., 2015). Moreover, the deficiency and sufficiency of vitamin D have a direct impact on immune responses (Aranow, 2011). With the fast spread of the novel SARS-CoV-2, authorities are suggesting vitamin D supplementation to strengthen the immune system (Grant et al., 2020).

A prominent antigenic enzyme related to immune regulation, signal transduction, and apoptosis is enzyme is DDP4 (dipeptidyl peptidase-4), which is also known as adenosine deaminase complexing protein two or CD26 (cluster of differentiation 26). DDP4/CD26 is expressed on the surface of most cell types and is responsible for the cleavage of X-proline dipeptides from the N-terminus of polypeptides. The spike glycoprotein of COVID-19 has an affinity for the human DPP-4/CD26 protein, thus reducing its immune regulatory activities and affecting signal transduction capabilities (Vankadari and Wilce, 2020). It is shown that the alteration in the structure of the DPP-4/CD26 receptor can be reduced by optimum vitamin D level (Komolmit et al., 2017). The hypothesis correlating COVID-19 with vitamin D status is supported by many clinical studies. Some recent reviews suggest that Vitamin D plays a major role in reducing the risk of acute respiratory viral infections such as para-influenza and Respiratory Syncytial Virus (RSV) (Zdrenghea et al., 2017). Some studies have also indicated that COVID-19 increases the concentration of pro-inflammatory cytokines leading to pneumonia, C-reactive protein (CRP), pneumonia, ARDS, and heart diseases (Huang et al., 2020b; Zhou et al., 2020b; Wang et al., 2020a). Moreover, it has been reported that patients suffering from immunodeficiency, bronchiectasis, and older age people with a minute deficiency of vitamin D are considered at higher risk of getting COVID-19 infection (Ebadi and Montano-Loza, 2020). In the US (Chicago), in most of the COVID-19 cases, around 70% of fatality is observed in people with the origin of African-American were at a higher risk of vitamin D deficiency (Ebadi and Montano-Loza, 2020).

Improved immunity against severe respiratory viral infections relies on high vitamin D levels (Bergman et al., 2013; Autier et al., 2017; Rejnmark et al., 2017). In addition, some studies have demonstrated that treating COVID-19 patients with high doses of vitamin D (250,000–500,000 IU) gave stable relief to mechanically ventilated, critically ill patients, and hemoglobin blood-carrying capacity was enhanced (Ebadi and Montano-Loza, 2020).

2.2. Role of vitamin A in immunity and protection from viral infections

Vitamin A encompasses a group of fat-soluble retinoids with antioxidant activities and plays a vital role in the proper functioning of the body, such as vision, reproduction, immune function, protection of epithelium, and cellular communications (Huang et al., 2018). It has been reported that Vitamin A is an essential component for the regulation of mice gene expression and optimum production of intestinal IgA in the body (Komolmit et al., 2017; Miroliaee et al., 2018). It is observed in randomized clinical trials that there is a reduction in the rate of morbidity and mortality by maintaining an optimal level of vitamin A (Mazumder et al., 2015).

In an etiopathogenesis of influenza study, it was shown that normal physiological concentration of retinoids appears to inhibit viral influenza infections in patients. However, it also showed that host resistance and susceptibility depend on the ratio of vitamin D to vitamin A: low ratios increase the risk of severe complications of the disease. In the same study, it was shown that the severity of infection was connected to pre-existing liver disease, diabetes, and obesity. A possible explanation is liver dysfunction and/or changes in retinoid metabolism (Mawson, 2013). In children, the supplementation of vitamin A has shown positive enhancement in an antibody response after viral infections such as measles and ant-rabies vaccination (Aglipay et al., 2017; Huang et al., 2018). There is no report on the effect of Vitamin A on COVID-19, which warrants new research that could benefit patients.

2.3. Role of vitamin E in immunity and protection from viral infections

Vitamin E is a broad term used for lipid-soluble compounds, including tocopherols (α-, β-, γ-, and δ-tocopherols) and tocotrienols (α-, β-, γ-, and δ-tocotrienols) (Brigelius-Flohé, 2021). It is a potent antioxidant with the capability to modulate host

immune functions (Brigelius-Flohé, 2021). Vitamin E significantly reduces the oxidative stress generated by binding free radicals and reactive oxygen species (Galmés et al., 2018; Aitken et al., 2022). Vitamin E insufficiency is associated with weakened and altered responses to humoral and cellular immunity (De La Fuente et al., 2020). It has been reported that low levels of vitamin E could increase the risk of infectious diseases such as pneumonia (Hemilä, 2016). Vitamin E deficiency has no relation to reducing the risk of respiratory infections (Pae and Wu, 2017). However, it is noteworthy that deficiency of vitamin E and D status in calves leads to bovine coronavirus infection (Nonnecke et al., 2014).

2.4. Role of vitamin C in immunity and protection from viral infections

Ascorbic acid is a known powerful antioxidant having the capability of boosting blood antioxidant levels (He et al., 2013; Wang et al., 2020a). The consumption of vitamin C increases in the body through physical exercise, thus increasing the antioxidant level in the blood, regulating gene expression and cell signaling, and enhancing skeletal muscle force production (Wang et al., 2020a). Vitamin C facilitates physiological reactions (hormone production and collagen synthesis) as an enzymatic co-factor in the body (Popovic et al., 2015). Studies in mice have shown that vitamin C can enhance the immune system in viral infections such as influenza A infection; the production of interferon-a/b is increased significantly in the early stages of the infection (Popovic et al., 2015). Some clinical trials have indicated that 26% of COVID-19-related pneumonia patients were transferred to the ICU because of Acute respiratory distress syndrome (ARDS) and shock complications (Kim et al., 2013). Recent research conducted in the US believes a reduction in the mortality rate in 167 patients with sepsis-related ARDS if administration of ~ 15 g/day of IV vitamin C continuously for four days (Truwit et al., 2019). Vitamin C uplifts the immune system and gives protection from infection caused by a coronavirus (Hemilä, 2016). One of the studies has reported that vitamin C facilitates the resistance of chick embryos in tracheal organ culture to avian coronavirus infection (Hennion and Hill, 2015). A significant decrease in the severity of pneumonia in patients is believed to be caused by the supplementation of vitamin C, and it is also believed that it might reduce the risk of lower respiratory tract infection under specific conditions (Gonzalez et al., 2018). According to the literature, COVID-19 has been reported to cause lower respiratory tract infection; therefore, vitamin C would be one of the best choices for the treatment of COVID-19.

3. Trace element's role in the immunity

Trace elements are important in physiological processes and contribute to the proper functioning and strengthening of the immune system. The sufficiency/deficiency of trace elements can greatly influence the functions of the immune system, such as antibody responses, cell-mediated immunity, and natural killer (NK) cell activity (Maggini et al., 2007).

The role of some trace elements in the regulation of the immune system and the regulation of various physiological processes in relation to viral infections are discussed below.

3.1. Zinc

Zinc is a dietary element that plays a major role in developing immune cells to strengthen both innate and adaptive immune systems (Maares and Haase, 2016). The human body cannot store zinc; therefore, any deficiency of zinc leads to a quick impact on the body. Zn deficiency leads to a decrease in the number of T and B-lymphocytes in both the thymus and bone marrow, which ultimately results in a weakened immune system and causes an increased risk of viral infections and cancer (Wessels et al., 2021). It has been found in the literature that zinc-deficient individuals are more prone to viral infections such as HIV or HCV (Read et al., 2019). A comparative study has shown that children (1 month-5 years old) suffering from pneumonia have become significantly stable in oxygen saturation and reduction in duration of fewer hours by the zinc supplementation (Acevedo-Murillo et al., 2019). At a specific intracellular concentration of zinc with some zinc-ionophores, some strands of RNA viruses become fragile, stopping their replication in the body (Maio et al., 2021). It is very important to note that a combination of zinc with pyrithione at minute concentration is helpful to discourage the replication of SARS coronavirus (SARS-CoV), and therefore, zinc supplementation could be used to decrease the severity of COVID-19 infections (Te Velthuis et al., 2010).

3.2. Magnesium

Magnesium is the second most abundantly intracellular cation and is essential for proper human body function (Barbagallo and Dominguez, 2015). The human bone contains 50%-60% magnesium and is considered the main storage reservoir for magnesium (Fiorentini et al., 2021). Magnesium has a remarkable role in immune functions by improving immunoglobulin synthesis, immune cell adherence, antibody-dependent cytolysis, macrophage response to lymphokines, and T helper-B cell adherence (Acevedo-Murillo et al., 2019). More interestingly, some studies have demonstrated that magnesium strengthens the immune system and reduces the risk of viral infection (Chaigne-Delalande et al., 2013). More recently, a study found that older COVID-19 patients were treated with a combination of Vitamin D-Magnesium-Vitamin B12 (DMB). This regimen significantly reduced the proportion of patients with clinical deterioration requiring oxygen support and/or intensive care support. [A cohort study to

evaluate the effect of a combination of Vitamin D, Magnesium, and Vitamin B12 (DMB) on progression to severe outcomes in older COVID-19 patients (Tan et al., 2020).

3.3. Copper

Copper is an essential micronutrient for the protection of both pathogens and host viral infections. Copper has a supportive and facilitative role as it improves the functioning of T helper cells, B cells, neutrophils, natural killer cells, and macrophages. These blood cells are related to the fight against viral infection and the production of antibodies (Elmadfa and Meyer, 2019). The deficiency of copper includes a reduction in white blood cells, immune responses, abnormal cellular functions, and connective tissue abnormalities (Elmadfa and Meyer, 2019). Copper is a potent antioxidant, and it has the capability to neutralize various single, and double-stranded DNA/RNA viruses, both enveloped or non-enveloped, such as bronchitis virus, poliovirus, human immunodeficiency virus type 1(HIV-1) (Reeves and DeMars, 2006). Some of the studies have significantly shown the inactivation of the nucleic acid strands of human coronaviruses by Cu alloys (Cu/Zn brass) by the production of ROS on Cu alloy surfaces (Kampf et al., 2020). However, there is no evidence that could support the therapeutic role of copper in the reduction of severity of COVID-19, but the dietary or therapeutic Cu supplementations may strengthen the immune function and improve the activities of other micronutrients that will be useful in preventing viral infection. Therefore, we can argue that the supplementation of Cu is crucial for preventing COVID-19 infections.

3.4. Selenium

Selenium is another trace element found in the human body and has a wide range of multiple activities, ranging from antioxidant effects (redox signaling and redox homeostasis) to antiviral inflammatory effects (Rayman, 2012). As selenium is an integral part of many selenoproteins, such as glutathione peroxidases and thioredoxin reductase, selenium has a significant role in protection from viral infections (Guillin et al., 2019). Selenium deficiency leads to several viral infections and the probability of high rate mortality increase and weakness in the immune system (Ivory et al., 2017). Moreover, some studies have demonstrated that a high concentration of selenium decreases the risk of antiviral effects (Rayman, 2012). It has been reported that supplementation of selenium in the deficient state could be a platform for the prevention and treatment of viral infections (Bermano et al., 2021). An increase in the virulence of some mild strains of the influenza virus has also been reported in selenium-deficient mice due to viral genetic mutation (Beck et al., 2003). The decrease in the virulence of viral infections can be attributed to selenium, which supports and enhances the function of a group of enzymes along with vitamin E. This collaboration helps reduce the formation of free radicals and prevents oxidative damage to tissues (Bermano et al., 2021). Selenium is more useful in combination with ginseng stem-leaf saponins, inducing an immune response to a live bivalent infectious bronchitis coronavirus vaccine in chickens (Ma et al., 2019). Therefore, selenium supplementation could be considered for the prevention and treatment of novel COVID-19.

3.5. Iron

Iron is a trace element found in the human body and required for both host and pathogen. Hyperion status decreases the efficiency of the immune system. The optimum level of iron is highly important for the proper functioning of immune responses, and the insufficiency of iron leads to oxidative stress, which ultimately leads to harmful viral gene mutations (Wessling-Resnick, 2018). Iron deficiency is also reported to have a central role in the propagation of current acute respiratory tract infections.

3.6. Implications for clinical practice

The clinical practice of understanding the role of vitamins and trace elements in immunity is fundamental to promoting optimal health and preventing infectious diseases. Vitamins such as vitamin C, vitamin D, and vitamin A, along with essential trace elements like zinc and selenium, play crucial roles in supporting the immune system. Vitamin C is known for its antioxidant properties, which help protect immune cells from damage caused by free radicals. Vitamin D is essential for the proper functioning of immune cells and has been linked to a reduced risk of respiratory infections. Vitamin A is involved in the maintenance of mucosal surfaces, acting as a barrier against pathogens. Zinc is a cofactor for various enzymes involved in immune function, and selenium is necessary to produce antioxidant enzymes. Deficiencies in these micronutrients can compromise immune responses, making individuals more susceptible to infections. In clinical settings, healthcare professionals assess and address patients' nutritional status, considering the impact of diet and supplementation on immune function. Integrating a comprehensive understanding of the role of vitamins and trace elements in immunity allows for targeted interventions and personalized approaches to enhance immune health and overall well-being.

4. Diagnosis methods

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly contagious zoonotic virus and is a global challenge that needs fast and rapid diagnostic testing. To date, there is no therapeutic

drug, and early-stage diagnosis is important to reduce the severity of the viral infection and its spread (Zhang et al., 2020). COVID-19 spread mainly through aerosol, human-to-human contagious transmission. Testing for active infection is important in the control of the spread of the SARS-CoV-2 virus by identifying infected individuals and contact tracing. To limit human-to-human transmission, patients are quarantined for a 14-day period or until the virus is cleared from the patient's body. However, rapid, precise, and accurate detection is required for effective control of COVID-19 in a community. In this review, we discuss available diagnostic techniques which are currently being applied.

4.1. Real-time reverse-transcriptase polymerase chain reaction (RT-PCR)

Real-time reverse-transcriptase polymerase chain reaction (RT-PCR) is an ideal and gold standard test that has been widely used for the detection and quantification of genetic materials (Bachman, 2013).

RT-PCR is a modification of PCR in which reverse transcription of RNA to DNA is performed for amplification. In other words, PCR is used for pathogens that already contain DNA for amplification, while RT–PCR is used for those containing RNA that needs to be transcribed to DNA for amplification. Both techniques are real-time, and the results are almost immediate.

RT-PCR is used to measure the abundance of RNA both qualitatively and quantitatively (Sanders et al., 2014). RT-PCR technology is being used for the detection and confirmation of viral RNA of SARS-CoV-2 with high precision (> 90%) (Corman and Drosten, 2020) and is highly reliable and accurate (Pillonel et al., 2020). It can produce test results in 3 to 6 hours. However, some studies have reported that the sensitivity of RT-PCR is less, ranging from 30-60 percent, including the limitation of sample collection and kit performance (Hennion and Hill, 2015).

In the RT-PCR test, saliva or mucous is collected from the suspected patient's nose or throat and treated with some chemical to remove fats, proteins, and other unwanted materials, leaving only bare RNA behind. The separated RNA is a mixture of the patient's genetic materials and viral RNA. The information of the viral RNA is then copied into a complementary DNA (cDNA), from which billions of the original RNA strands are produced.

The detailed sequence is shown in Fig. 1 (Shahi et al., 2018). In practice, a standard RT-PCR usually completes in 35-45 cycles to amplify the viral RNA. A fluorescent probe is used to identify the amplified viral DNA, and the intensity of the fluorescence emission is used to quantify the presence of viral RNA in the patient's sample. The threshold value is optimized by the number of successive cycles performed by the PCR machine for the estimation of viral load. RT-PCR is a well-documented technique with high precision and accuracy, but it can only confirm the current viral infection. Fig. 2 shows that each cycle contains three steps (annealing of primers to the DNA template, extension of the DNA, and DNA denaturation) and illustrates the exponential nature of the reaction. Reproduced with permission of ref (Santos et al., 2004).

RT-PCR-based SARS-CoV-2 diagnosis is expensive, slow, and requires sophisticated equipment and trained personnel, making it unsuitable for point-of-care testing. It is also unsuitable for the detection of previous infections, as the virus is present in the body for a limited time. The knowledge of past infections is used to comprehend the development and spread of the virus, particularly for asymptomatic cases.

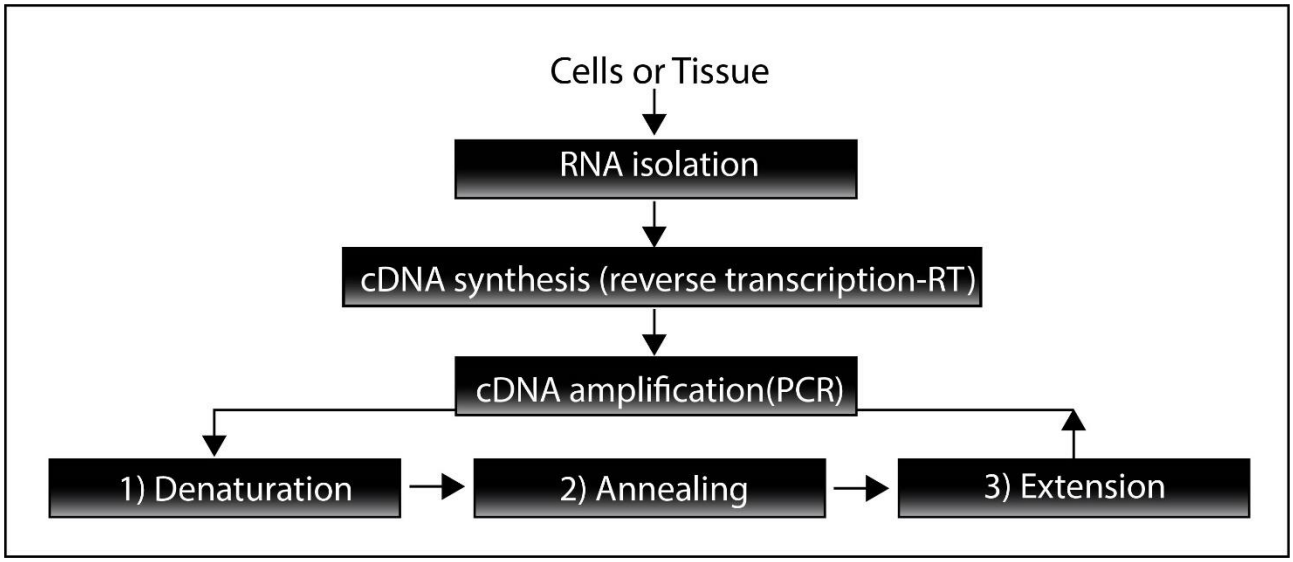

Fig. 1: Schematic representation of PCR (Shahi et al., 2018)

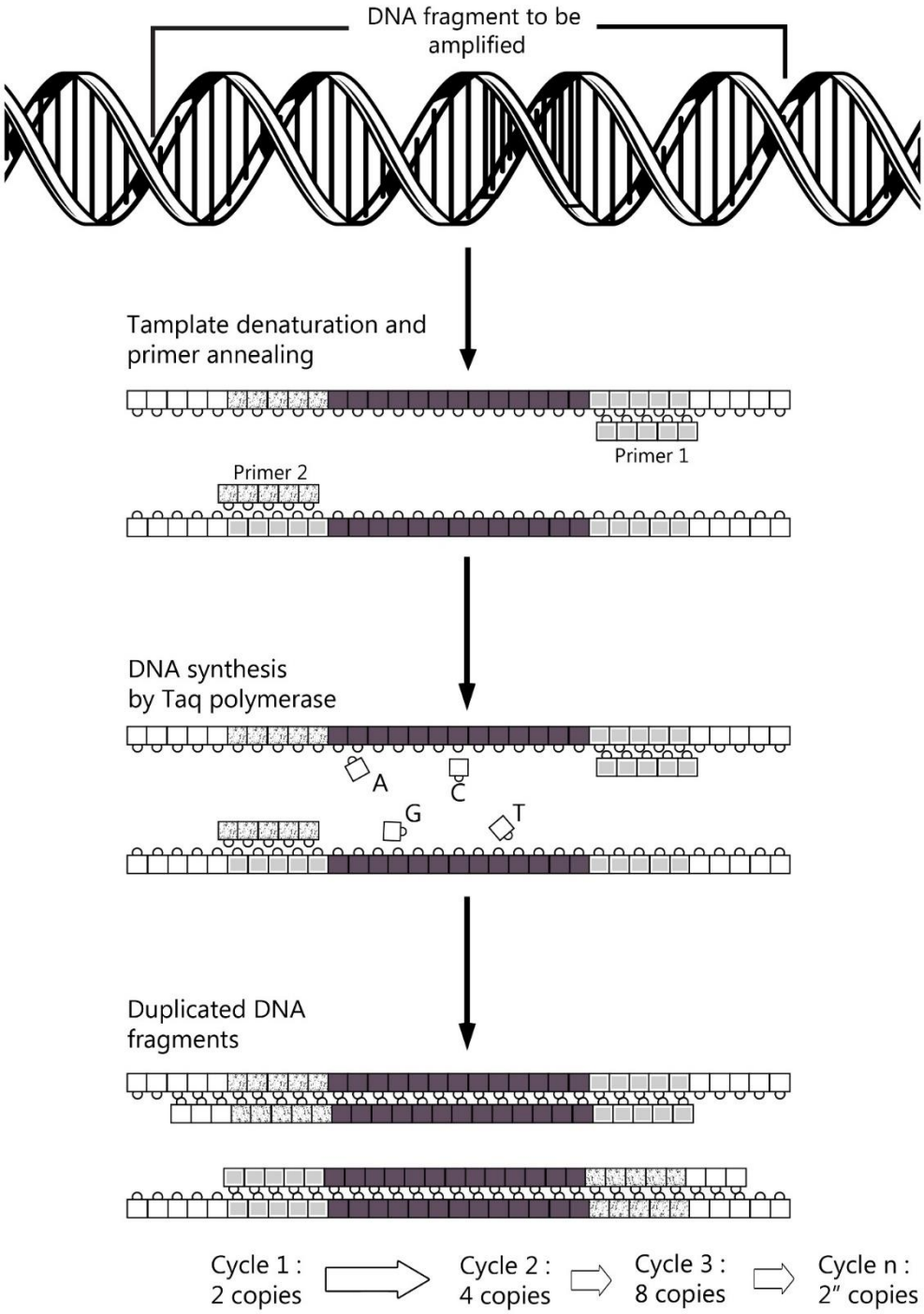

Fig. 2: Schematic diagram of PCR

4.2. Loop-mediated isothermal amplification (LAMP)

Loop-mediated isothermal amplification (LAMP) is a single-tube technique with outstanding identification of DNA and other diseases (Wang et al., 2015). Unlike RT-PCR, LAMP is a newer and more advanced technology that allows DNA amplification at constant temperature (60-65 °C) and does not require a thermal cycler. The use of an enzyme- DNA polymerase that possesses strand displacement activity in the replication process of DNA is the key principle of LAMP assay. This property is an advantage as no heat is required for the denaturation of double-stranded DNA, which allows primer annealing and subsequent amplicon elongation. LAMP is a robust technique that produces fast results (<30 minutes) and is highly tolerant to sample matrix inhibitors.

In the LAMP test, the sample is collected from the patient's nose or throat. Similar to RT-PCR, the targeted sequence of viral RNA is converted to cDNA and amplified at a single temperature (60-65 °C) using four primers (F1P-forward inner primer, F3-forward outer primer, B1P-backward inner primer, and B3-backward outer primer) and polymerase enzymes facilitating the replication. The use of four primers and two additional loop primers (FL-forward loop primer and BL-backward loop primer) can recognize six distinct regions on a target gene and thus increases the specificity of the LAMP test as compared to conventional RT-PCR and PCR (Soroka

et al., 2021). The enzymes used in LAMP are less sensitive to inhibition than Taq polymerase as they can work with minimally processed target samples.

The amplification of viral DNA employing LAMP technology is confirmed from the reaction mixture by measuring turbidity caused by magnesium pyrophosphate precipitate in solution as a byproduct of amplification (Soroka et al., 2021). The appearance of turbidity in the reaction mixture can be visualized by the naked eye and does not require the intervention of a machine to interpret the results. To confirm and quantify the viral RNA in the patient's sample, the turbidity of the reaction mixture is measured, or fluorescent species are added that bind the copied DNA, and the intensity of emission confirms the quantification of viral DNA (Hardinge and Murray, 2019). LAMP is a robust technique widely used in developing countries for the detection of infectious diseases such as malaria, tuberculosis, and SARS-COV-2 (Thapa et al., 2019; Lamb et al., 2020). The detection of viral RNA by using LAMP assay is summarized in Fig. 3.

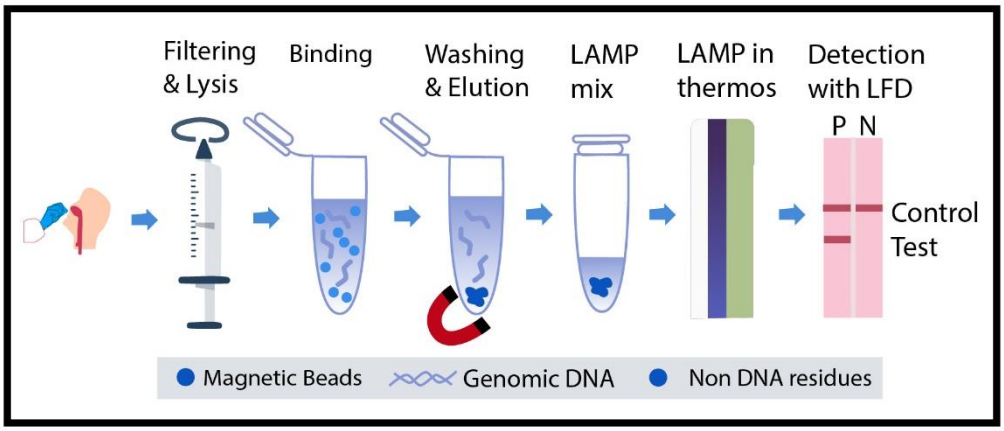

Fig. 3: schematic representation of LAMP assay (Yang et al., 2017)

LAMP is a low-cost alternative to polymerase chain reaction (PCR) technology and can rapidly generate large quantities of amplified material within 15-25 mins. However, due to the nature of the method, it cannot be used for the detection of previous COVID-19 infections.

4.3. Lateral flow/ colloidal gold immunochromatography

Lateral flow assay (LFA), also known as Colloidal gold immunochromatographic test strip (CG-ICTS), is a common antibody test used for the detection of antibodies to a disease in a patient's body fluid. Lateral flow assays are unidirectional and are used for qualitative and quantitative detection of antigens, antibodies, and products of gene amplification (Rohrman et al., 2012). Biological samples such as urine, saliva, sweat, serum, plasma, and other fluids can be tested by employing this method (Magambo et al., 2014; Carrio et al., 2015; De Giovanni and Fucci, 2013). LFA test uses the same principal and technology as the pregnancy test and can detect active viruses through the presence of virus antibodies in the patient's sample. Colloidal Gold is a qualitative membrane-based immunoassay for the detection of COVID-19 antibodies (IgG + IgM) in whole blood, serum, or plasma. The method is versatile as test kits developed for SARS-CoV-2 can be used directly by patients themselves and do not require medical/technical expertise. LFA produces quick results and is cheap, with clinical sensitivity and specificity as high as 98%. It also allows visual positive or negative results. Many commercial diagnostic companies have developed lateral flow tests for SARS-CoV-2. Lateral flow immune assays for COVID-19 are a simple device that directly detects antibodies in the blood.

The device contains a series of polymeric strips with specific such as the SARS Cov-2 antibodies to which antigens can get attached and detected. The test sample is placed on the sample pad, which is made of cellulose or glass fiber, which allows transport of the sample by capillary action in a smooth and homogeneous manner to the other components. The second component is the conjugate pad, where labeled biorecognition molecules (typically antibodies labeled with non-colloidal gold particles) are placed. As the sample flows through the conjugate pad, the labeled conjugate is immediately released upon contact with the moving liquid. Materials such as glass fiber, cellulose, and polyester are used to manufacture the conjugate pad. The complex formed by the antibody and antigen then travels to the detection zone. This zone contains a highly porous nitrocellulose membrane designed with specific biological sections (containing either antibodies or antigens) distinguished by immobilized lines. However, the sensitivity of the assay can be enhanced if the bio reagents are properly dried and dispensed. Their role is to react with the analyte bound to the conjugated antibody and capture on the test and control line. The binding and capturing of antibodies to the test and control line results in color change, which necked eyes can visualize (Xu et al., 2014). The adsorbent pad facilitates the unidirectional liquid flow over the membrane, thus preventing the backflow of the sample. All these components are fixed and organized over the backing card (Fig. 4).

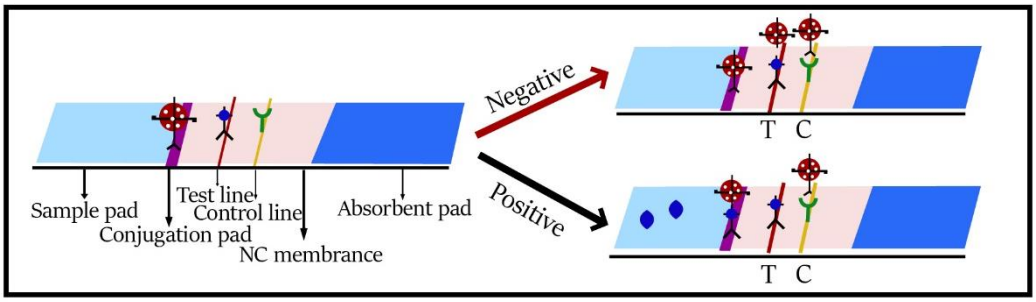

Fig. 4: Schematic representation of lateral flow assay (Shi et al., 2018)

There are two types of LFA: sandwiched assays and competitive assays.

4.3.1. Sandwiched assays

Sandwiched assays are more generally used for large analytes as they have more binding sites. In the conjugate pad, the virus comes into contact with the antibody, which contains the visual tag, and a tagged antigen/antibody complex is formed. The latter migrate, under capillary action, to the test-line, where it binds to an immobilized specific antibody, where it binds for a second time and is retained and accumulates. A visual change occurs, which can be measured and quantified. Fig. 5a summarizes the sandwiched assay mechanism.

4.3.2. Competitive assays

Competitive assays are commonly used for small analytes with fewer binding sites. The strategy used here is the opposite of the sandwiched one, in the sense that only negative results give a colored response at the test line. The samples first encounter antibodies with a visual tag, and an antibody-antigen complex is formed, which migrates to the test-line. The test line has viral antigen immobilized on its surface. If the sample contains a viral antigen, the antibody-antigen complex will pass through the test-line without any visual signal. Conversely, if the sample is negative, then the tagged antibodies from the conjugate pad will form an antibody-antigen at the test-line and produce a colored response. Fig. 5b summarizes the competitive assay mechanism.

LFA does not follow the amplification of viral RNA step and, therefore, is suitable for the detection of past infections. It is a quick test, producing results in 15-30 minutes, but the technology is new, and no evidence for the accuracy of coronavirus diagnosis.

4.4. Enzyme-linked immunosorbent assay (ELISA)

The enzyme-linked immunosorbent assay (ELISA) is a bioanalytical assay widely used for detecting and quantifying antigens, hormones, antibodies, and glycoproteins in a biological sample. In the ELISA test, the enzyme liked to antibody, having the potential of attachment to the molecules being detected and identified, leading to the formation of fluorescent products. The intensity of fluorescence is measured by a fluorimeter (spectrophotometer) machine. The change in the fluorescence intensity is used to detect and quantify the sample of interest. Rapid and accurate results in COVID-19 diagnosis are very important, as are serological assays. ELISA is considered an accurate and efficient method for the detection and identification of antibodies (IgM and IgG) against SARS-CoV-2 (Liu et al., 2020). The antibody detection test can be performed in a single tube by mixing the antibody, antigen, enzymes, and patient sample along with fluorescent markers. There are three types of ELISA.

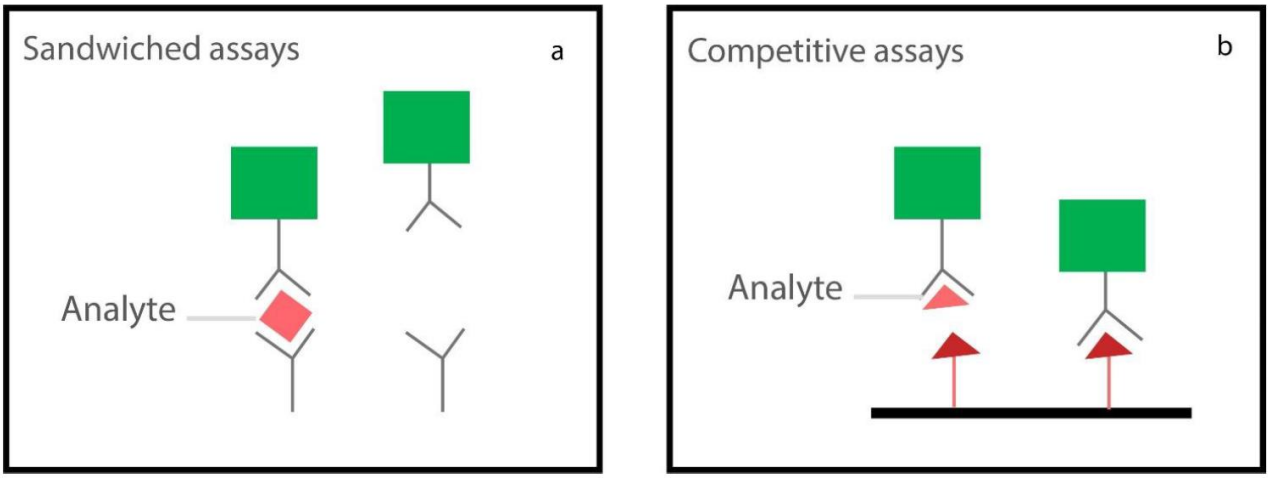

Fig. 5: Schematic representation of sandwiched assays and competitive assays

4.4.1. Indirect ELISA

Indirect ELISA involves the following steps: First, a patient's blood or serum, which may contain antibodies against SARS-CoV-2, is added to a tube containing the SARS-CoV-2 antigen. The antibodies specific to SARS-CoV-2 bind to the protein that is anchored at the bottom of the tube while the rest of the sample is washed away. Next, secondary antibodies, which are linked to enzymes and produced in a laboratory, are introduced. These secondary antibodies attach to the patient's antibodies already present in the tube. Any excess of the enzyme-linked secondary antibodies is then washed off to ensure specific binding. A special fluorescent molecule is added to the mixture. If the patient's sample contains antibodies to the virus, these antibodies will interact with the enzyme-linked secondary antibodies, causing a color change. This color change, indicative of a positive result, can be observed with the naked eye or measured using a spectrophotometer. If the patient's blood does not contain the virus, the enzyme-linked antibodies will not bind, resulting in no color change, which confirms a negative result.

It is believed that an ELISA antigen test can also be developed to detect current COVID-19 infection. The schematic representation of indirect ELISA is shown in Fig. 6.

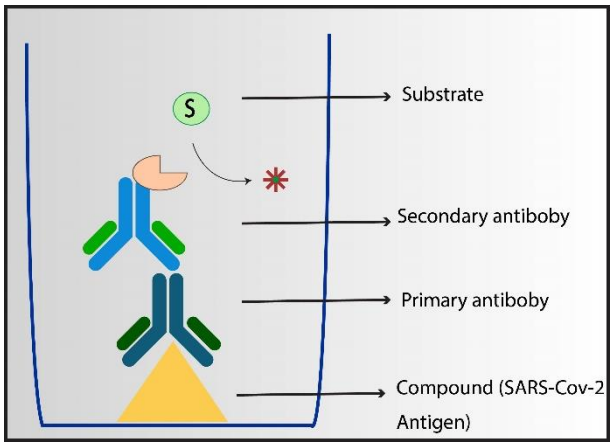

Fig. 6: Schematic representation of indirect ELISA assays

4.4.2. Direct ELISA

Direct ELISA includes the following steps. The Compounds (antigen) of interest are attached to the bottom of the tube. Enzymes linked to antibodies bind with the compound (antigen). The unknown antibodies are removed by washing.

In the next step, the substrate is added, which is transformed into the color product by the enzyme-linked antibody. The intensity of the color is measured by a calorimeter. The schematic representation of direct ELISA is summarized in Fig. 7.

4.4.3. Sandwiched ELISA

In the sandwiched ELISA, the antibody is fixed onto the bottom of the tube. The Compounds (antigen) specific to the antibody bind to the antibody that is fixed at the bottom of the tube. The Primary antibody binds another epitope of the compound (antigen). Then, the mixture is washed to remove unwanted materials.

In the last step, enzymes linked secondary antibody is added and binds to the primary antibody. The substrate is converted into fluorescent species. The schematic representation of the sandwiched assay is concluded in Fig. 8.

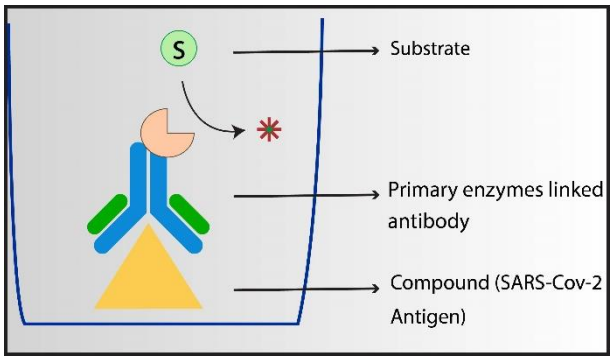

Fig. 7: Schematic representation of direct ELISA assays

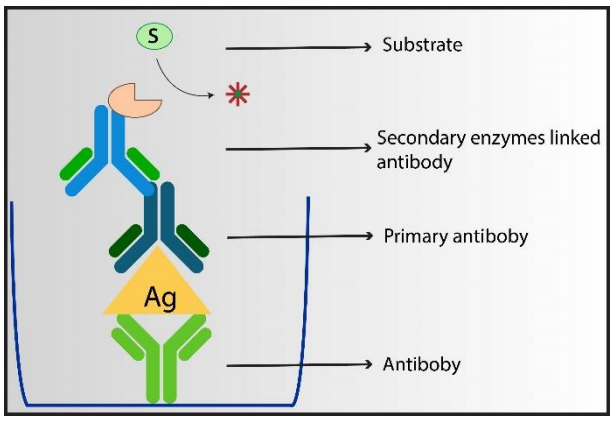

Fig. 8: Schematic representation of sandwiched ELISA assays

Handling unknown viral infections is consistently challenging, and various techniques have been employed to manage these infections. Rapid and early detection is crucial for addressing viral pandemics effectively. Each developed technique has its specific strengths and weaknesses. The techniques for viral detection discussed above are summarized in Table 1.

Table 1: Summary of RT-PCR, LAMP, LFA, and ELISA assays

Technique	Thermal cycler	Time	Primer	Sensitivity	Visual detection
RT-PCR	Required thermal cycler	> 1 hour	2 primer required	Sensitive to sample matrix inhibitors	No visual detection
LAMP	Not-required thermal cycler	<1 hour	6 primer required	Tolerant to sample matrix inhibitors	Visually detected
LFA	Not-required thermal cycler	5-30 min	No primer required	Sensitive to reagents and biomolecule	Visually detected
ELISA	Not-required thermal cycler	1-3 hours	No primer required	Sensitive to reagents and biomolecule	Visually detected

4.5. Comparison of diagnostic techniques

The various diagnostic techniques for detecting SARS-CoV-2 have been discussed, each with distinct characteristics. Real-time reverse-transcriptase polymerase chain reaction (RT-PCR) stands out as the gold standard, offering high precision (>90%), but is hindered by its expense, time-consuming nature, and the need for sophisticated equipment and trained personnel. Loop-mediated isothermal amplification (LAMP) presents a rapid and cost-effective alternative with a quick turnaround (<30 minutes) and tolerance to sample matrix inhibitors. Lateral flow assays (LFA) excel in simplicity, providing rapid results (15-30 minutes) and versatility for qualitative and quantitative antigen or antibody detection, but their effectiveness may vary, and evidence for coronavirus diagnosis accuracy is still emerging. Enzyme-linked immunosorbent assay (ELISA) is acknowledged for its accuracy in detecting antibodies against SARS-CoV-2, offering efficient serological assays. However, each method has limitations, such as RT-PCR's inability to detect past infections, LAMP's unsuitability for such detection, and the novel nature of LFA technology lacking extensive evidence for coronavirus diagnosis accuracy. The selection among these techniques should consider the specific diagnostic needs, resource availability, and the intended application setting, emphasizing the need for a nuanced approach in evaluating their practical applications.

5. Vaccine

The SARS-CoV-2 pandemic is a global crisis and has not yet been resolved properly. One of the most effective strategies, similar to our history of success in combating highly contagious diseases to save a life, is to design a highly efficacious and safe vaccination in which known risk is weighed against prospective benefit. However, building a strong vaccine candidate that is both safe and effective for human administration necessitates a significant amount of time and work. In this part of our review, we have focused on vaccination pre-clinical and clinical data for several vaccine candidates and reviewed any available data of these candidates in different human populations and conditions.

5.1. ChAdOx1 nCoV-19 adenoviral vector vaccine

At the very beginning of the SARS-CoV-2 pandemic, ChAdOx1 nCoV-19 developed at Oxford University and consisted of a replication-deficient chimpanzee adenoviral vector containing the SARS-CoV-2 spike protein gene. In mice and rhesus macaques, it has been found to elicit a strong humoral and cell-mediated response. Rhesus macaques were likewise protected against SARS-CoV-2-induced pneumonia after being vaccinated with ChAdOx1 nCoV-19 (van Doremalen et al., 2020). In animal models, one dosage of this vaccine has been proven to induce antigen-specific antibody and T-cell responses, whereas the second dose has been demonstrated to augment antibody responses and increase SARS-CoV-2 neutralizing antibody (Graham et al., 2020). Very similarly, in Phase I/II trial, researchers found that two doses of the vaccine increased anti-spike protein neutralizing antibody titers, Fc-mediated functional antibody responses, antibody-dependent neutrophil/monocyte phagocytosis, complement activation, and natural killer cell activation, supporting the use of two doses in later clinical trials (Barrett et al., 2021). Another Phase I/II trial found that this vaccine has a good safety profile and can elicit antibody responses in the majority of people 19. Similarly, the Phase II/III study revealed that this vaccine is well tolerated and capable of eliciting immunogenicity in the majority of trial participants (Ramasamy et al., 2020). Based on previous studies, an interim analysis of the efficacy and safety of ChAdOx1 nCoV-19 vaccine combining four clinical studies has also been published (Voysey et al., 2021). The vaccination demonstrated an excellent safety profile, with major adverse events and special interest adverse events evenly distributed across the research arm. The study's limitations include the inclusion of younger age groups and a higher proportion of white and female individuals, who are generally at a reduced risk for serious illness.

5.2. BNT162b2 mRNA vaccine

Prior to the COVID-19 pandemic, no mRNA medication or vaccine had been approved for human use. BioNTech and Pfizer collaborated on BNT162b2. It's a full-length spike protein encoded by a lipid nanoparticle-formulated nucleoside-modified RNA. Among the four possible mRNA vaccine options, this vaccine candidate was chosen for future clinical development based on evidence of its capacity to elicit neutralizing antibodies with a decreased incidence and severity of systemic responses (Walsh et al., 2020). There were eight instances of COVID-19 found among 17,411 individuals in the vaccination arm, and 162 cases of COVID-19 were discovered among 17,511 participants in the control arm in the Phase III trial, resulting in a vaccine effectiveness of 95%. The local reactions were mild to moderate in severity and dissipated in 1 to 2 days, with no participant reporting a grade 4 local response after the two injection doses. Systemic reactions, such as fever and chills, appeared 1 to 2 days after immunization and disappeared quickly. Treatment-related adverse events were reported by 21% more individuals in the vaccination arm (21%) than in the control arm (5%), with this increase owing mostly to the inclusion of transitory occurrences. Only four vaccination-related severe adverse events were recorded in the vaccine arm, and no fatalities were linked to the vaccine (n = 2) or placebo (n = 4) by the investigators. The short follow-up period, with a median follow-up of only two months after the

second dose, is one of the report's major flaws, as is the fact that the research did not examine whether immunization reduces asymptomatic infection.

5.3. mRNA-1273 mRNA vaccine

Moderna mRNA-1273 encodes the S-2P antigen, which consists of the SARS-CoV-2 glycoprotein with a transmembrane anchor and an intact S1-S2 cleavage site, which was co-developed by researchers at the National Institute of Allergy and Infectious Disease. The robustness of mRNA-1273 in generating SARS-CoV-2 neutralizing action, protecting upper and lower airways as well as the lungs, was demonstrated in animal research (Corbett et al., 2020). mRNA-1273 was able to generate anti-SARS-CoV-2 immune responses in all subjects in a Phase I research, with no trial-limiting safety concerns (Jackson et al., 2020). The vaccine's safety profile was also examined in older individuals, with the majority of adverse events being mild or moderate (Anderson et al., 2020). The Phase III trial enrolled 30,420 people, with 185 instances of COVID-19 found in the control arm and 11 cases in the vaccination arm, yielding a vaccine effectiveness rate of 94.1 %. In the vaccination arm, unspecified adverse events at the injection site were more common than in the control arm. Nonetheless, they were mostly of Grade 1 or 2 intensity and lasted just 2-3 days on average after the first or second dose. Solicited systemic adverse responses were more common in the vaccination arm than in the control arm, and the severity of the systemic events increased in the second dosage compared to the first dose, although the effects persisted only 2-3 days on average after the first or second doses. The frequency of unintentional adverse events, severe adverse events, and serious adverse events recorded within the 28 days following injection, on the other hand, was nearly the same in the vaccination and control groups. The short period of safety and effectiveness follow-up time, similar to the previous two vaccine candidates, is a major drawback of the recently reported data, with a median follow-up time of only two months at the time of data cutoff. At the time of data collection, there was also no assessment of asymptomatic infection. Despite this, mRNA-1273 generated a high degree of binding and neutralizing antibody responses in a Phase I study, according to an update of the immunogenicity data. Although these reactions decreased slightly over time, they remained high in all 34 healthy adult individuals assessed 90 days following the second immunization. These findings show that mRNA-1273 might offer long-term humoral immunity (Widge et al., 2021).

5.4. Ad26.COV2.S adenovirus vector vaccine

Janssen is the company behind Ad26.COV2.S. It's a full-length SARS-CoV-2 spike protein encoded by a recombinant replication-incompetent adenovirus serotype 26 vector. The vaccine was shown to be safe in Phase I research, with just 5 out of 401 individuals reporting significant side events and no one dropping out due to an adverse event. Furthermore, neutralizing antibodies were found in all individuals, indicating that Ad26.COV2.S immunization was highly immunogenic (Sadoff et al., 2021). The findings of the Phase I study justify the vaccine's admission into a Phase III trial. A preliminary review of 468 symptomatic COVID-19 cases revealed that this single-dose vaccine had a vaccine effectiveness of 66 percent in avoiding moderate and severe COVID-19 at 28 days post-vaccination, according to Phase III research.

5.5. NVX-CoV2373 protein subunit vaccine

Novavax's NVX-CoV2373 vaccine comprises Matrix-M1 adjuvant as well as a recombinant SARS-CoV-2 full-length wild-type spike glycoprotein. The vaccine has been evaluated in a variety of animal models, and its capacity to induce immunogenicity and offer protection against SARS-CoV-2 infection has been established in these animal models (Guebre-Xabier et al., 2020; Tian et al., 2021). The vaccine was shown to be safe and produced adequate immune responses in a Phase I trial (Keech et al., 2020). Following up with a Phase III trial in the UK, the vaccination effectiveness was shown to be 89.3 percent overall and 86 percent against the newly discovered variation B.1.1.7.

5.6. CoronaVac inactivated virus vaccine

CoronaVac is a Sinovac-inactivated viral vaccine that stimulates an immune response against several antigens of the SARS-CoV-2 virus rather than only the spike protein. The effectiveness and safety of this inactivated viral vaccine were tested by healthcare professionals in a Phase III double-blind placebo-controlled clinical study that used a two-dose intramuscular injection schedule with a 14-day gap. Although the results of this Phase III research have not yet been published in a peer-reviewed publication, Phase II data revealed that seroconversion of neutralizing antibodies was greater than 97 percent with an adverse response rate of less than 35 percent (Zhang et al., 2021).

The company also revealed results from its Phase III study, which showed vaccination effectiveness of 51% for all cases, 84 percent for patients requiring medical care, and 100% for severe fetal cases and cases requiring hospitalization.

6. Future prospects

The COVID-19 pandemic is unparalleled, and early detection is critical to limiting the spread of this infectious disaster. Considering the time-consuming nature of the PCR technique, new advancements and technological approaches are being developed to enable rapid and efficient diagnosis. To manage the pandemic caused by SARS-

CoV-2, several molecular techniques have been recently suggested to ensure early diagnosis with high precision and accuracy. These include loop-mediated isothermal amplification (LAMP) and lateral flow immunoassay for detecting SARS-CoV-2 RNA. Recombinant DNA technology is also believed to offer a platform for rapid screening and diagnosis of the virus. Furthermore, serological assays are proving useful as tools for early-stage detection, which helps prevent viral spread. It is crucial to understand the dynamics of SARS-CoV-2 viral and antibody interactions to optimize current assays and address ongoing technical challenges in detecting minor and asymptomatic infections. Future insights into the pathogenicity of COVID-19 and improvements in test technology could enhance the sensitivity, selectivity, and effectiveness of existing diagnostic systems.

Based on the rate of morbidity and mortality caused by COVID-19, a suitable platform is desirable for the development of a vaccine and research into potential pharmaceutical treatments that can significantly reduce the infection of SARS-CoV-2 in humans.

7. Conclusion

It is very regretful to say that a lot of the world population will contract SARS-CoV infection. While specific treatment is still under trial, individual preventive and protective measures drive the personal risk of getting the disease. Among the virus-infected hosts, their different metabolic statuses, as determined by many factors such as diet, nutrition, age, sex, medical conditions, lifestyle, and environmental factors, govern the personal fate toward different clinical severity of COVID-19. The individual assessment of the possible dietary, nutritional, lifestyle, and environmental risks, together with proper risk management, is the sensible way to deal with the SARS-CoV-II pandemic (we need to work on it).

In conclusion, the progression and impact of SARS-CoV-2 are influenced by the interactions between the virus and an individual's immune system. This relationship also depends on several viral factors, such as the type of virus, mutations, viral load, and the virus's viability in vitro. Factors related to the individual's immune system include genetics (such as HLA genes), age, gender, nutritional status, neuroendocrine-immune interactions, and physical condition. These elements collectively determine whether an individual becomes infected, the duration and severity of the illness, and the potential for reinfection. At the initial stages of the COVID-19 epidemic, accurate diagnosis was deemed crucial for controlling disease spread. Developing new, safe, accurate, rapid, and simple technologies for detecting SARS-CoV-2 remains a critical challenge. Physicians aim to intervene in these factors to steer them towards outcomes beneficial to human health, aiding in patient recovery. However, it is overly optimistic to assume that medical interventions can guarantee a 100% cure rate.

Compliance with ethical standards

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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