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Review Article
COVID-19: A Review on the Role of Trace Elements Present in Saudi Arabian Traditional Dietary Supplements

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Abstract
The novel coronavirus infection is also called COVID-19 (coronavirus disease 2019). The infection has affected millions of people worldwide and caused morbidity as well mortality in patients with pre-existing chronic conditions such as metabolic, respiratory and cardiovascular disorders. The severity of the disease is mostly seen in people with low immunity and chronic sufferers of respiratory, cardiovascular and metabolic disorders. To date, there is no specific treatment available for COVID-19. Precaution and prevention are the most recommended options followed for controlling the spread of infection. Trace elements such as zinc, calcium, iron and magnesium play an important role in boosting the immunity of the host system. These components assist in the development and functioning of lymphocytes, cytokines, free radicals, inflammatory mediators and endothelial functioning. This review summarizes the common dietary supplements that are regularly consumed in Saudi Arabia and are known to contain these vital trace elements. Data available in Google Scholar, NCBI, PUBMED, EMBASE and Web of Science about COVID-19, micronutrients, trace elements and nutritional supplements of Saudi Arabia was collected. By highlighting the traditionally used dietary components containing the essential elements, this review could provide useful knowledge crucial for building immunity in the population.

Key words: COVID-19, immunity, trace elements, dietary supplements, population

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The world health organization has declared 2019 the novel coronavirus infection as a pandemic. The disease has infected millions of people causing mortality worldwide. Saudi Arabia reported the first COVID-19 (coronavirus disease 2019) positive case in March and is now one of the most affected countries in the region[1]. The virus belongs to the same family that caused Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV) but possess a higher rate of infectivity[2].

Research suggests that COVID-19 causes serious complications in people who have compromised immunity and co-morbidity. Pneumonia is considered to be the major and frequent serious manifestation that progresses to multi-organ failure, arrhythmias, septic shock and death[3].

Evidence from earlier studies suggests that products of natural origin when used as dietary substances facilitate microflora and supports innate immunity[4,5]. On contrary, intake of excess animal foods depletes the level of good bacteria and also enhances abnormal inflammatory processes leading to metabolic, pulmonary, cardiovascular and renal diseases[6]. Further, natural products rich in essential nutrients, minerals, trace elements are reported to be useful in combating coronavirus infection. Vitamin C (1-4 g/day), vitamin D (2000 IU/day) and zinc (25 mg/day) have been established to maintain the activity of the immune system in reducing the complications as well preventing the development of the infection. These components are involved in the production, activation, regulation and signalling of immune cells[7-10].

Several researchers have indicated the benefits of natural medicine, vitamins and trace elements in the management of infectious diseases including those affecting the respiratory system[11]. A previous study suggested that natural supplements containing vitamin C, vitamin D, zinc, magnesium, etc., showed the immunity-boosting property and significantly reduced the viral load[12].

Vitamin A was reported to act on retinoic acid-inducible gene I (RIG-I) and tripartite motif 2 and 22 genes to induce the production of antibodies[13]. Vitamin B complex, on the other hand, is reported to diminish the synthesis of several pro-inflammatory mediators such as IL-1β, IL-6, TNF-α, viral replication process and oxidative stress[14,15]. Vitamin C obtained from the diet is essential for the biosynthesis of several enzymes. Vitamin C plays an active role in neutrophil and monocyte recruitment and chemotaxis during the state of infection[16]. It is also essential for the proliferation of lymphocytes, immunoglobulin's and diminishes the free radical and cytokines levels[17].

Vitamin D is mainly responsible for calcium homeostasis[18]. It is also reported to enhance immunity and blocks the cytokine storm that is known to be the major cause for COVID-19 complications. In a recent study, it was observed that vitamin D deficiency enhanced the COVID-19 virulence due to activation of Papain-like protease (PLpro)-mediated replication, dipeptidyl peptidase-4 receptor binding, modification in the M-protein mediated type-1 IFN and RIG-I[19,20]. Likewise, vitamin E participates in the regulation of immune activity and is one of the potent non-enzymatic antioxidant agents[21].

Saudi Arabia has one of the oldest histories of human civilization. The vast regions of the country have different climatic conditions that support the growth of several plants used traditionally as medicine[22]. Some of them are regularly used by the local population in the preparation of food and were also found to possess therapeutic activities[23]. In the absence of an established treatment for COVID-19, enhancing the dietary intake of those natural supplements that augment the host defence are reported to be one of the approaches towards management of the COVID-19 complications[24].

In this direction, the present review summarizes the common dietary components used in Saudi Arabia such as the sage leaf, ajwain, chamomile, anise, laurel leaf, marjoram, olive leaves and thyme. These natural products were known to possess antimicrobial properties and also contain the essential trace elements that might improve immunity[25]. The review could provide the scope for investigating the potentiality of common dietary supplements of Saudi Arabia in overcoming the COVID-19 difficulties.

Search method: Online review of the literature was conducted in PubMed, Google Scholar and Science Direct websites using the keywords such as 'COVID-19', 'Immunity', 'Trace elements', 'Saudi Arabia', 'Dietary supplements' and 'Nutrition'. The review was conducted between April and May 2021. The review resulted in 1242 total articles. However, only 36 articles were selected for the present study. The authors independently reviewed the titles, abstracts and text of the articles. The information such as English language, scientific content, study design, route of administration, chemical analysis, biochemical estimation and statistical tests were considered the critical parameters for evaluating the content[26].

COVID-19 and its pathogenesis

Coronavirus: Coronavirus disease/COVID-19 belong to a family of single-stranded RNA virus called Coronaviridae. The subfamily of this includes four genera called alpha, beta, delta and gamma coronavirus. The first two genera are known to infect the mammals and the latter two cause the disease in

avian[27]. The infection due to coronavirus is reported to produce mild symptoms except for SARS-CoV, MERS-CoV and SARS-CoV2 (COVID-19). These three viruses can cause more serious respiratory tract infections including fatalities. The genomic sequencing of COVID-19 suggested that the virus has a close evolutionary relationship with SARS-CoV[2].

Coronavirus transmission from animals: The pieces of evidence collected so far suggests that the COVID-19 was transmitted from bats, more precisely from horseshoe bats. Although, the source of SARS-CoV as well the MERS-CoV was found to be bats, but an intermediate host has been suspected that might have caused the mutation so that the virus crossed over to mammals. Palm civets could have acted as the intermediate host for SARS-CoV, while dromedary camels for the MERS-CoV[28]. In the case of COVID-19, several species such as pangolin, snakes and turtles have been suspected to be the intermediate host before the virus jumped from bats to humans. The genomic analysis suggested that pangolin could be the most likely intermediate host as they are illegally imported into China[29].

COVID-19 transmission from one person to another: Droplets coming from an infected person's mouth, nose during speaking, sneezing or coughing are considered to be the main route of transmission. The fine mist from the infected person can be carried up to 10 m. Inhalation of these infected mists or droplets in family, community gatherings, crowded places and hospitals could transmit the virus to the healthy person. Hence, the infection is now considered to be more an air-borne[30]. However, infection through contaminated surfaces, saliva, stool, urine and sexual intercourse has also been reported[31].

What are the symptoms of COVID-19?: A meta-analysis of a total of 43 studies indicated that symptoms such as fever, cough and fatigue are frequent, shortness of breath, myalgia, sore throat, headache, chills are common whereas rhinorrhea, diarrhoea, vomiting, anosmia and hypogeusia are less common[32]. Medical complications and mortality are few but can be seen in elderly people with acute respiratory distress syndrome and coronary heart disease. Complications due to COVID-19 are associated with sepsis, respiratory heart failure and shock. Although COVID-19 can affect people of all age groups, complications in children and adolescents are found to be rare[33].

Response of immune system to COVID-19 infection: The infection of COVID-19 is divided into three phases, asymptomatic, non-severe symptomatic and severe respiratory symptomatic. The available data suggests that only a small fraction of people will show severe forms of infection like respiratory and multi-organ failure. The COVID-19 virus enters the host cell by binding to angiotensin-converting enzyme-2 (ACE2) and releases its RNA for replication[34]. The infection of the virus will trigger both innate and adaptive immune responses; however, the severity of the response varies depending on the phase(s) of infection. In mild to moderate forms of infection, the levels of activated CD4+ helper T cells, CD8+ killer T cells, IgG and IgM antibodies were found to be elevated[35]. However, the level of these immune cells was found to be depleted in the severe form of infection, but instead, the level of pro-inflammatory cytokines and chemokines such as tumour necrosis factor-α, interleukins, macrophage, inflammatory protein-1 α were enhanced. The hyperactive inflammatory response due to cytokine storm is known to cause devastating effects on the respiratory system of the patients leading to respiratory failure, septic shock, multi-organ failure and death[36].

COVID-19 and the role of trace elements : Since ancient times, the traditional methods of healing are practised worldwide. These methods include the use of plant-based medicines, minerals, dietary components and animal products[37]. In the absence of specific treatment for COVID-19, the traditional way of treating a disease assumes importance. As per the literature, the pandemic that affected mankind in the past has been effectively defeated by traditional practices. These ancient medicines are known to contain several phytochemical micronutrients such as flavonoids, alkaloids, sterols and essential trace elements. All these components are reported to work synergistically to cause bio-molecular changes in the host cells[6,7]. The trace elements such as Zn, Ca, Mg, Fe and Se are reported to modulate the functioning of host cells including the immune system[38]. The following sections summarize the role of trace elements in immunity.

Zinc: Zinc plays its role in immunity by acting as an essential element in the development and functioning of T and B lymphocytes. The deficiency of zinc is known to affect the non-specific immunity such as polymorphonuclear, the functioning of natural killer cells and complement activity[10,39]. Zinc deficiency is also found to damage the natural barriers for the entry of pathogens such as gastrointestinal and respiratory mucosa. The functioning of macrophages, cytokines and phagocytes also depends on zinc availability[40]. In addition, zinc is reported to act against free radicals and serves as a cofactor for several enzymes involved in the cytolytic activity of foreign particles[41].

Zinc also plays a role in the T-lymphocyte maturation, cytotoxicity and production of cytokines such as IL-2. The deficiency of zinc is linked to frequent respiratory infection as well in the production of pro-inflammatory cytokines such as IL-6, IL-8 and TNF-α[42]. Exogenous supplementation of zinc is reported to decrease the severity of viral infections. Zinc reduces the entry of virus, inflammatory process and other complications associated with it. The presence of zinc ions has shown an inhibitory effect on the viral RNA polymerase activity[43]. Clinical studies have suggested that supplementation of zinc has reduced the COVID-19 symptoms besides improving the blood oxygen level. Moreover, intake of zinc reduces the co-morbid complications due to metabolic diseases such as diabetes, obesity, hypertension and hyperlipidemia[44].

Calcium: Calcium is reported to play several vital functions in the body that are directly as well indirectly mediate immune activity. Calcium is one of the essential elements required in the production of antibodies[18,45]. Further, the changes in the cytoplasmic concentration of calcium are known to activate lymphocyte production, generation of free radicals and neutrophil degranulation. Calcium ions, in addition, function as the second messenger in leukocyte and lymphocyte cell signalling[46].

The data from clinical studies suggest that COVID-19 infection disturbs calcium homeostasis. The patients severely affected by the infection were found to have low calcium levels, probably due to disturbances in calcium absorption, alteration in parathyroid hormone level and vitamin-D regulation[47].

Magnesium: The role of magnesium in the body is again important since it is involved in several functions such as nucleic acid synthesis, protein synthesis, neuromuscular signal conduction, regulation of blood glucose and blood pressure[5,48]. Magnesium also plays a significant role in immune function. The deficiency of magnesium is reported to cause a reduction in T cell synthesis, increased inflammatory cytokines and endothelial dysfunction. Together, these could be manifested as compromised vascular integrity, reduced CD4+ and CD8+ T cells and suppression of inflammatory process associated with chronic metabolic disorders such as diabetes, hypertension, obesity, stress and ageing[48,49].

In affected patients with COVID-19, the administration of magnesium is shown to reduce the collagen deposition, hyperactivity and wheezing of lung tissues. Additionally, magnesium reduces the formation of plasmin and inhibits thrombosis, which is considered to be one of the leading causes of hospitalization[50].

Iron: This essential nutrient is required for most living organisms. The mineral is needed for transportation of gases, electron transport system and catalysis of several important intracellular reactions such as DNA replication. The deficiency of iron is mostly manifested as anaemia[51]. Patients with iron deficiency have been associated with higher susceptibility to viral infection and mortality. Hence, it is always recommended to monitor the levels of iron in patients infected with COVID-19[52].

Trace elements and herbal dietary supplements in Saudi Arabia: According to National Center for Complementary and Integrative Health, dietary supplements such as herbs, vitamins, minerals, probiotics are referred to as natural products. Traditionally, these substances are popular and are consumed worldwide as folk medicine[22,53]. In Saudi Arabia, the natural way of treating diseases is practised in different regions. Natural substances are regularly used for treating diseases such as hyperlipidemia, diabetes mellitus, wound healing, pain, inflammation, digestive, respiratory, nervous and urinary system. The popularity among the tribal community is immense since they are reported to be safe and devoid of major side effects[54]. Some of these are also used in the preparation of culinary to enhance the taste and flavour of food. The following section summarizes some of the important dietary supplements known to contain the essential elements and are frequently used in Saudi Arabia.

Sage leaf: The botanical name of the plant is *Salvia officinalis* and belongs to the family Lamiaceae. The plant is a perennial, evergreen shrub with blue to purplish flowers. It is a member of the mint family and has culinary use in the Arab peninsula region. It is used traditionally as a flavouring agent in the preparation of food and is also used as hot black tea[55]. The plant was reported to contain several essential trace elements such as Zn (247 mg kg^{-1} of crude drug), Ca (429 mg kg^{-1}), Fe (430 mg kg^{-1}) and Mg (1467 mg kg^{-1}). The medical research suggests that the phytoconstituents present in the plant possess anti-inflammatory, memory enhancing, anti-cancer, wound healing, antidiabetic, mood-elevator, antihypertensive and digestive properties[55,56].

Ajwain: The plant is called *Trachyspermum ammi* belonging to the family Apiaceae. The leaves and seeds are edible. The seeds are used for aromatic purposes in cooking. Sometimes, the seeds are sprinkled over bread and biscuits. Seeds are pungent and bitter and known to contain Zn (185 mg kg^{-1}), Ca (345 mg kg^{-1}), Fe (159 mg kg^{-1}) and Mg (556 mg kg^{-1})[57]. The extracts of the seeds are reported to possess antimicrobial, anti-hyperlipidemic, anti-inflammatory,

anti-hypertensive, anti-peptic ulcer, anti-microbial, relieves indigestion, prevents coughing and improves air-flow[58].

Chamomile: The plant scientifically called *Matricaria chamomile* and belongs to the family Asteraceae. The extract is used in breweries due to the presence of flavouring components. Chamomile tea is a herbal tea made from dried flowers and hot water and is consumed in many regions of the world[59]. The medicinal benefits of chamomile tea include reduction in menstrual pain, treating diabetes mellitus, preventing osteoporosis, reducing inflammation, cancer treatment, sleep induction, mental relaxation, treatment of symptoms of cold and skin disorders such as vitiligo[60]. The extract is known to contain Zn (190 mg kg^{-1}), Ca (323 mg kg^{-1}), Fe (360 mg kg^{-1}) and Mg (981 mg kg^{-1})[59,60].

Anise: The plant is called *Pimpinella anisum* and belongs to the family Apiaceae. The plant is a flavouring plant, the aroma and flavour of the seeds have similarities with other herbs such as fennel and liquorice. The seeds are frequently used to flavour the food, confectionaries and herbal teas. The essential trace elements present in the seeds include; Zn (194 mg kg^{-1}), Ca (497 mg kg^{-1}), Fe (355 mg kg^{-1}) and Mg (1503 mg kg^{-1})[61]. The medicinal properties reported due to the presence of active ingredients are anti-depressant, anti-ulcer, anti-microbial, relieve menopause symptoms, wound-healing, anti-hyperglycemic and anti-inflammatory[62].

Laurel leaf: The plant scientifically known as *Laurus nobilis*, belongs to Lauraceae. The plant is an aromatic evergreen tree with green, glabrous smooth leaves. The leaves are frequently used for seasoning during cooking procedures. Grounded leaves can be ingested safely often as soups. Dried leaves are used as robust spices and the wood of the plant can be burnt for getting a strong smoke flavour[63]. The essential oils of the leaves are known to provide respiratory relief, regulate menstrual flow, relieve pain, heal wounds, supports digestion, promote hair growth. The vital trace elements include, Zn (244 mg kg^{-1}), Ca (2677 mg kg^{-1}), Fe (2480 mg kg^{-1}) and Mg (1011 mg kg^{-1})[63,64].

Marjoram: It is a perennial herb with sweet pine and citrus flavour. The plant is called *Origanum majorana*, belonging to the family Lamiaceae. The plant in many countries considers as a symbol of happiness. The leaves are commonly used to garnish soups, salad and meat dishes. The decoction of the leaves is also used as herbal tea[65]. The plant is reported to possess several medicinal properties such as antioxidant, anti-inflammatory, anti-microbial, alleviate digestive issues, regulate the menstrual cycle and hormones. Marjoram extract is known to contain several essential micro-nutrients and trace elements such as Zn (232 mg kg^{-1}), Ca (301 mg kg^{-1}), Fe (451 mg kg^{-1}) and Mg (1280 mg kg^{-1})[65,66].

Olive leaves: The botanical name of the plant is *Olea europaea*, belonging to the family Oleaceae. Fruits are the most popular and are used in several forms of dishes including bakery products. The oil is equally popular and is used as a cooking medium both for taste as well as for medicinal properties. The plants are grown in many countries commercially and are considered to be one of the oldest existing plants in the world[67]. The leaves of the plant are also quite popular and are used in cooking purposes for flavouring properties. Some of the important health benefits of olive leaves include; treatment of hyperglycemia, hypertension and viral infections such as herpes, influenza, HIV. These medicinal properties are related to several phytoconstituents and trace elements present in the extract. The important trace elements reported in olive leaves are Zn (171 mg kg^{-1}), Ca (568 mg kg^{-1}), Fe (177 mg kg^{-1}) and Mg (2467 mg kg^{-1})[68,69].

Thyme: The dried aerial parts of the plant are commonly used in traditional methods of cooking. The evergreen aromatic leaves give a flavour of mint. The botanical name of the plant is *Thymus vulgaris* and belongs to Lamiaceae. The plant is cultivated mostly in mountainous highlands. It is used to add flavour to the food, garnish the food and also as a hot beverage[70]. The extract of the plant is reported to contain several vital trace elements such as Zn (215 mg kg^{-1}), Ca (150 mg kg^{-1}), Fe (1587 mg kg^{-1}) and Mg (871 mg kg^{-1}) required for maintaining the homeostasis of the host system. The reported medical properties of the plant are anti-bacterial, anti-hypertensive, anti-tussive, immunity booster and mood elevator. And these have been linked to the presence of several active constituents present in the plant[71].

CONCLUSION

The complications associated with COVID-19 are mostly observed in low immune and comorbid patients. Trace elements play an important role in boosting the activity of immune cells. Traditional dietary supplements are used since ancient days to treat several diseases including microbial infections. This review summarized the common herbal dietary components of Saudi Arabia that contain vital trace

elements and were also found to be effective in treating microbial and other comorbid conditions. Research in this direction might explore nutrition-based interventions in the prevention and management of COVID-19.

SIGNIFICANCE STATEMENT

"This study discovered that trace elements play a vital role in building the host immunity system. Since, COVID-19 complications were observed mostly in immune-compromised patients, increase intake of dietary supplements rich in trace elements could benefit the population in the management of COVID-19 related complications. Traditionally several natural substances containing trace elements were commonly used as dietary supplements in Saudi Arabia. However, their true potential in the management of infectious diseases such as COVID-19 is yet to be explored. Information from this study could provide a new direction for researchers to evaluate the therapeutic benefits of dietary supplements popular in Saudi Arabia".

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