

BIOACTIVE COMPOUND AND NUTRITIONAL INTERVENTION OF CORONAVIRUS-19 PATIENTS

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Abstract

The data presented in this review article is aimed to support research on COVID-19, the symptoms, transmission, prevention, and immune boosting methods against this deadly virus. It is need of time to search for alternative treatment methods to control the spread of COVID-19. Traditional food and medicinal plants contain a large number of ingredients which can increase the immunity in addition to their antiviral properties. Nutritional intervention such as vitamin A, B, C, D and E help to strengthen immune system. The Omega-3 polyunsaturated fatty acids are important mediators of the adaptive immune responses and precursors of the resolvins/prolactin, leukotriene and prostaglandin respectively. Minerals such as, zinc, selenium and iron are important for the development and maintenance of immune cells of innate and adoptive immune system. Bioactive intervention including polyphenolic compound including myricetin, scutellarein, quercetin, silvestrol, caffeic acid display reasonable levels of inhibition activity of COVID-19 helicase and Silvestrol subclass of flavonoid prevented the translation of HCoV-229E proteins specific RNA helicase. Alkaloid such as, tetrandrine, fangchinoline, cepharanthine and tryptanthrin have anti-inflammatory, immunologic and anti-allergic effects and Tryptanthrin subclass of alkaloid is effective in inhibiting the early and late stages of the HCoV-NL63 replication and blockage of post entry of HCoV replication. Terpenoid such as Saikosaponin inhibits the viral penetration and attachment. Protein such as lecithin and Griffithsin are the most important inhibitors of MERS-CoV. The decoction of *Syzygium Aromaticum*, *Zingiber officinale Roscoe*, *Piper nigrum linn*, *Sudarshana Ghana vati*, *Curcuma longa*, *Chauvan prasha* participate in various processes of the adaptive/innate immunity. Dietary food supplements such as citrus fruits (orange, lemon, grapes), apple, sitaphal, papaya, green leafy vegetable such as, broccoli, garlic, onion; ginger, nuts, pepper, turmeric, egg yolk, mushroom, shellfish are good for fighting against various diseases.

Keyword: COVID-19, food, Nutrition, Bioactive compound, medicinal plants, vitamin, minerals.

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Introduction

Coronavirus-19 (COVID-19) belongs to the subfamily Orthocoronavirinae and family of Coronaviridae and further classified as α -corona virus, β -coronavirus, γ -coronavirus [1]. COVID primarily reason due to the enzootic infection in the mammals and birds and in the last decade it was shown to cause infection in the human being as well [2]. The transmission evidence from human to human has been confirmed among closed contact [3]. The genetically COVID-19 (coronavirus disease 2019) genome is single stranded positive RNA. The Sequence of COVID-19 possessed typical genome structure belong to the cluster of β -coronavirus including middle east respiratory syndrome- coronavirus (MERS- CoV) and severe acute respiratory syndrome (SARS)-CoV [4]. COVID-19 outbreak was started in the December 2019 in Wuhan, the capital of central China's Hubei Province [5] [6]. The COVID-19 was confirmed in Pakistan on 26 February 2020 when a student tested positive in the Karachi who was returned from Iran. The COVID-19 209300 Cases have been confirmed in the Pakistan at date on 1 July 2020 with recoveries

98500 and 4300 deaths [7] [8]. The most common clinical symptoms are fever, cough and nonspecific symptoms headache, dyspnea, fatigue and muscle soreness [9]. The global health emergency was declared on January 30, 2020 by World Health Organization [10]. As clinical physician, virologist, epidemiologists, phylogeneticists and another policy makers and public health officials have been trying to understand pathogenesis of COVID-19 diseases and its spreading. Some investigators have investigated imaging pattern on chest radiographs, and CT Scans [11].

1. Symptom of COVID-19:

The COVID-19 infectious disease appears after an incubation period of approximately 5.2 days [12]. The COVID-19 symptoms period from beginning to death range between 6 to 41 days with the median 14 days. The COVID-19 period is depends on the age of COVID-19 patient and status of immune system. Shortest period was observed in the age of above 70 years old patient as compared to others [13]. The COVID-19 common Symptoms at onset of illness including dry cough, fever, fatigue, headache, sputum

production, diarrhea, hemoptysis, lymphopenia and dyspnea^{[14], [15], [9], [16]}. Serious symptoms: shortness of breath, difficulty breathing, chest pain or pressure, loss of movement and speech. Less common symptoms: diarrhea aches, pain, headache, discoloration of finger and toes, sore throat, conjunctivitis, rash skin, loss of smell and taste^[17].

2. Transmission of COVID-19: The COVID-19 was exposed to wet animal market in the Wuhan city, the capital of central China's Hubei Province where live animal were sold routinely, that was likely zoonotic origin. Efforts have been made to find out a reservoir host or intermediate carrier from which disease may have spread to human being. The initial investigation reported that two species of snakes could be possible reservoir of the COVID-19. However, still there is no evidence reservoir of coronavirus other than birds and mammals^{[18], [19]}. Transmission from person to person has occurred due to direct contact or through droplets spreading during coughing and sneezing from infected COVID infected person. In few studies pregnant women in their third trimester were reported corona virus but there was no any evidence of transmission to child from mothers^{[20], [21]}

3. Prevention of transmission COVID-19

The corona virus transmission can be prevented due to regular hand washing with soap and water, clean with alcohol-based hand rub. Avoid touching face and cover mouth and nose with mask whenever coughing and sneezing, maintain distance at least 1 meter between person to person, stay at home and avoid traveling and stay away from large group^[17].

5. Nutritional intervention for COVID-19:

5.1 Vitamin C: Vitamin C (Ascorbic acid) is water soluble vitamin and play an important role to supports immune system functions and protects against corona virus infection^[22]. It was reported that Vitamin C amplified the resistance of chick embryo tracheal organ cultures to avian coronavirus infection^[23]. Three human controlled clinical trials had recorded that there was significant lower incidence of pneumonia in the Vitamin C supplemented trial groups and suggested that Vitamin C might prevent the vulnerability to reduce respiratory tract infectious disease under positive conditions^[24].

Dietary Sources of Vitamin C: The best dietary sources of Vitamin C include orange, orange juice, lemon, papaya, cantaloupe, asparagus, cauliflower, green pepper, broccoli, grapefruit, grapefruit juice, brussels sprouts, kale and strawberries^[25].

5.2 Vitamin B: Vitamin B is water soluble vitamin. It works as coenzyme. Vitamin B₃ also known as Niacin, significantly prevents neutrophil infiltration into the lungs with strong anti-inflammatory effects during ventilator made lung injury and controlled the development of significant hypoxemia^[26]. Vitamin B₆ is

also known as Pyridoxine, requires in protein metabolism and participates in more than 100 reactions in the body tissues. Vitamin B₆ plays important role in the immune system function. Deficiency of Vitamin B may lead to weak the host immune response. Vitamin B should be supplemented for enhancement of immune system to the virus infected patients^[22].

Dietary Sources of Vitamin B₃: The best sources of niacin including fish as halibut and tuna and meats such as chicken, pork and beef. Niacin enriched in the cereals including whole grains, legumes, fortified cereals, seeds and bread products. The coffee and tea are also good sources of Niacin while smaller amount present in the green vegetable and milk^[27].

Dietary Sources of Vitamin B₆: The excellent sources of vitamin B₆ present in the whole grain, meats, vegetable, banana, nuts and fortified cereals^{[28], [29], [30]}.

5.3 Vitamin D: Vitamin D is fat soluble vitamin. Vitamin D can be synthesized in the human body with help of sunlight. It plays important role in maintaining integrity of bone and stimulates the maturation of various cell including immune system cells. Low level of Vitamin D has been reported in healthy adults in mostly winter season^[31]. The COVID-19 was first investigated in the winter season of 2019 and frequently affected middle aged to elderly person. Coronavirus infected people might be Vitamin D deficient. A low Vitamin D status was reported in patient with infection of bovine coronavirus^[32].

Dietary Sources of Vitamin D: Vitamin D is present both in the plants and animals. Eggs yolk, beef, liver and veal, milk, butter, cheese and yogurt, saltwater fish such as salmon, herring, sardines and tuna, cereals, orange juices, bread and fortified food are good source of Vitamin D^[33].

5.4 Vitamin E: Vitamin E is fat soluble vitamin. Vitamin E plays an important role in the decreasing oxidative stress through binding to free radicals as an antioxidant^[34]. Vitamin E deficiency was recorded to strengthen the myocardial injury of coxsackievirus B₃ (kind of RNA virus) infection in the mice^[35]. An increased virulence of the coxsackievirus B₃ in the mice was observed, due to selenium and Vitamin E deficiency^[36].

Dietary Sources of Vitamin E: Vitamin E is found in the plant and animal foods. Plant foods especially oils from plants considered richest sources of Vitamin E. The richest sources of vitamin E is oil including sunflowers, canola, cotton seed, olive and safflowers. Soybean and corn oils possesses some α -tocopherol while considered higher amounts of the γ -tocopherol^{[37], [38]}.

5.5 Vitamin A: Vitamin A is fat soluble vitamin. β -carotene is plant derived vitamin A precursor. Vitamin A supplementation decreased, morbidity and mortality rate in the different infectious disease including malaria, diarrheal diseases, measles, measles related pneumonia

and human immunodeficiency virus infection. It also offered for protection against complication of other life-threatening infection including lung disease, malaria and human immunodeficiency virus [39]. The effect of infection by infectious bronchitis virus, a kind of coronavirus was marked in the chicken fed when a diet marginally vitamin A deficient than fed a diet adequate with vitamin A [40]. The mechanism of Vitamin A inhibits the measles replication and regulating the elements of the innate immune system response in the uninfected by stander cell and make them rebellious to productive infection during consequent rounds of viral replication [41]. Therefore, vitamin A could be good option for the treatment of coronavirus disease and prevention from lung infection.

Dietary Sources of Vitamin A: Vitamin A is found in the animal origin including fish such as herring, sardines, tuna, liver and dairy product including whole milk, butter, cheese. β -carotene is precursor of vitamin A. significant amount of β -carotene present in the orange, yellow and red colored vegetable and fruit including carrots, papaya, watermelon, squash, grapefruit, pumpkin, green vegetable, tomatoes and also tomato product ketchup, chilli sauce, spaghetti sauce [42].

5.6 Omega-3 polyunsaturated fatty acid: Omega- 3 is long chain polyunsaturated fatty acids (PUFAs). It is most important mediators of the adaptive immune system response and inflammation. The omega 3 and 6 polyunsaturated fatty acid are mostly possessed anti-inflammatory and pro-inflammatory effect. These are precursors of leukotrienes/prostaglandin and resolvins/protectins respectively [43].

Dietary Sources of omega-3 PUFAs: It is found in the oil including vegetable oil, nut oil, flax seeds, flax seed oil and also found in fish and leafy vegetable and some animal especially in grass fed animal [44].

5.7 Iron: Iron is most important mineral, which is required for the both host and pathogen. Iron deficiency impairs host immunity whereas iron overload causes oxidative stress to spread harmful viral mutations [45].

Dietary Sources of Iron: Fish, meat and poultry, nuts, vegetable, fruits and tofu are good dietary sources of iron. The dairy product including milk, eggs and cheese represent poor sources of iron [46].

5.8 Selenium: Selenium deficiency is induced the impairment of host immune system as well as rapid mutation of benign variants of the RNA viruses to virulence [47]. It was reported that deficiency of selenium increased the pathology of an influenza virus infection as well as drive to change in the genome of the coxsackievirus and guarantee the virulent virus to obtain virulence due to genetic mutation [48]. Therefore, selenium supplement could be effective for treatment of COVID-19.

Dietary Sources of selenium:The selenium content found in the plant and animal foods. Seafood represent

one of the better sources of selenium. Animal product (organ meats) contain range from 40 to 150 μ g/100g. cereals and grain contain over than 80 μ g/100g and less than 10 μ g/100g. Muscle meat contain 10 and 40 μ g/100g whereas dairy product contains less than 30 μ g/100g [49].

5.8 Zinc: Zinc is a trace mineral that plays key role for the development and maintaining immune system cells of both adaptive and innate immunity [50]. The deficiency of zinc may cause dysfunction of cell mediated and humeral immunity and increase weakness to infectious diseases [51]. The concentration of pyrithione and zinc at low concentrations which inhibits the replication of severe acute respiratory syndrome coronavirus (SARS-CoV) [52]. Therefore, supplement of zinc may have effect on COVID-19 related symptom including lower respiratory tract infection and diarrhea.

Dietary Sources of Zinc: The very good sources of zinc present in the red meat (organ meats), pork, dairy product, and seafood including mollusks and oysters while plants are good sources of zinc including whole grain (bran and germ) and vegetable (leafy and roots) [53].

6. Bioactive compound intervention for COVID-19

6.1 Polyphenols: Polyphenolic compound was investigated in several studies, with antiviral activities. Polyphenolic compound including scutellarin and myricetin displayed reasonable level of inhibitory activities again COVID helicase [54]. The bioactive polyphenolic compound was investigated in the ethanol extract of *Psoralea corylifolia* seeds which was responsible for against of SARS-CoV PLpro. The phenolic compound including neobavaisoflavone, bavachinin, isobavachalcone, 4-O- methylbavachalcone, corylifol A and psorralidin were isolated with their antiviral activities varying IC50 values between 4.2-38.4 μ M. The isobavachalcone and psorralidin indicated the greatest antiviral activities. It was found to be mixed reversible inhibitors of PLpro with type 1 mechanism. It binds to the free enzyme as well as enzyme substrate complex [55].

6.2 Flavonoid: Quercetin is subclass of flavonoid found in the many foods particularly high concentration in the herbs and berries. Their activity showed an IC50 of 8.6 μ M against COVID-19 [56, 57]. Silvestrol subclass of flavonoid is found in the *Aglaia sp.* that inhibitors of MERS-CoV replication EC50 of 1.3 μ M. The Silvestrol is a specific inhibitor of RNA helicase eIF4A and inhibitors of viral replication as well as inhibition of expression of CoV protein and inhibition replication/transcription complex formation [58]. It was reported that ethanol extract of stem of *Sambucus formosana* (elderberry) against human corona virus strain HCOVNL63, result moderately high effectiveness EC 50 of 1.17 μ M. for virus yield reduction. In the further study caffeic acid was investigated as most potent compound found to inhibit the attachment of HCoV to host cell and

indicating the binding to S protein. Caffeic acid also found to inhibit the other virus which cause hepatitis B [59]. The extract of *Sambucus nigra* (black elderberry) has been commercialized for treatment of cold and flu symptoms and considered therapeutic plasma concentrations for viral inhibition [60].

6.3 Alkaloid: The tryptanthrin is indole alkaloid derivatives that found a broad spectrum of biological activities including significant antiviral activities, anticancer, anti-inflammatory, antiallergic, antioxidant, antimicrobial and antiprotozoal activities [61]. Tryptanthrin is prevented the replication of the early and late stage of HCoV-NL63 and particularly blocking the viral genome synthesis and papain like protease 2 activity. As well as inhibiting the post entry stage of HCoV replication [62]. Another recent study bis-benzylisoquinoline alkaloids including Cepharanthine, fangchinoline and tetrandrine (CPE assay EC50 of 0.33 μ M, 1.01 μ M and 0.83 μ M) inhibited the HCoV-OC43 [63]. These are bioactive compounds investigated in the *Stephania tetrandra* plant related species. All bioactive compounds were investigated to inhibit virus induced death cell by suppressing viral replication. It is expressing viral N and S protein (Nucleoprotein) as well as virus induced host response whereas inhibitory effective concentration was not reported for the inhibition of viral protein expression or host response [64].

6.4 Terpenoid: Saikosaponin represent a group of pentacyclic triterpenoid derivatives usually present as glycosides, Saikosaponin was isolated from plants including *Scrophularia scorodonia*, *Heteromorpha spp*, and *Bupleurum spp*. Saikosaponin (A, B2,C and D) possesses anticoronavirus activities and their mode of action against HCoV-229E in vitro as well as against other several virus such as human immunodeficiency virus (HIV) [65], [66], [67]. All Saikosaponin identified as good to moderate anticoronavirus activity including Saikosaponin B2 showed greatest effectiveness EC50 of 1.7 μ M that inhibited viral penetration and attachment [68].

6.5 Saponin: Glycyrrhizin is a triterpene saponin with important biological and pharmacological properties including most active against SARS-CoV in vitro as well as modification of glycyrrhizin may create novel anti-SARS-CoV drugs. SARS-CoV-2 receptor bind domain could inter cell expression human cell ACE2 not any other receptors. Glycyrrhizin has recently indicated to have potential to bind to ACE2 and preventing the SARS-CoV infection [69]. Glycyrrhizin could reduce the activation of nuclear factor including C-Jun N terminal kinase (JNK), p38, kappa beta (NFkB) and redox sensitive signaling events that are required for virus replication [70].

6.6 Lectins: Lectin is protein that can bind reversibly and specifically to carbohydrate groups [71]. Lectin is another group of natural occurring compound which

inhibit SARS-CoV. It is indicated as antiviral agent against influenza and herpes simplex virus [72], [73], [74].

6.7 Griffithsin: Griffithsin is a protein that is isolated from red algae *griffithsia* possessed 121 amino acid sequence [75]. Griffithsin 12.7 kDa lectin present red algae *griffithsia* which is one of most important inhibitors of MERS-CoV. It encompasses three carbohydrate binding domain that allow to bind glycan on CoV protein points and inhibit viral attachment to cell of host with high potential in the vitro trial against MERS-CoV (EC50 of 0.125 μ M) [76].

The several bioactive such as flavonoid found in the medicinal plants are shown in the Table-1. That is reported antiviral activities These flavonoid included quercetin, kaempferol, catechin, luteolin-7-glucoside, curcumin, demethoxycurcumin, apigenin-7-glucoside, naringenin, oleuropein, , epicatechin gallate, gingerol, zingerol, and allicin were recommended; present in medicinal plants as potential inhibitors of COVID-19 [87], [88], [89]

7. Herbal intervention for COVID-19

The decoction of *Syzgium Aromaticum*, *Zingiber officinale* Roscoe, *Piper nigrum* linn, *Sudarshana Ghana vati*, *Curcuma longa*, *Chauvan pasha* that are provided humoral and cell mediated response [90], [91], [92]. Fatty acid in the form of ghee are concerned in the regulation of immune system function, control immune system and participate in various processes of the adaptive/innate immunity [93]. *Curcuma longa linn* has possessed bioactive compound as curcumin which blocks cytokine release and most significantly the key pro-inflammatory cytokines, interleukin-6, tumor necrosis factor- α and interleukin-1 that are recommended to take with milk. The cytokine suppression is released by curcumin associates with clinical enhancement in the experimental models of flu and infectious diseases and also compared with COVID-19 whereas a cytokine storm plays a important role in the mortality [94]. *Chauvan prasha* has been established beneficial in the treating problem of respiratory diseases including common cold, allergic cough, bronchitis and supports respiratory tract as immune-boosting agent [95]. In the table-2. It is indicated bioactive compound found in the medicinal plants which possessed best therapeutic tool to treat different viral disease including HSV-1, COVID-19, HCoV-NL63, herpes virus and corona virus [96].

Conclusion

Management of COVID-19 is a great challenge for the world community. As most reliable and effective management is being carried out by fluid therapy and oxygen support which is not excess able to less privileged class of world community and putting huge burden to the hospitals throughout the globe. It is the need of time to save lives within shorter period and effective manner with smaller cost and less burden. Therefore, it is suggested via this paper to encourage the

Use of various nutraceuticals that can boost the immune system and combat with this deadly disease.

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