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The use of Traditional Medicines, Vitamins, and minerals against COVID-19; a Review

Elmuaiz Gasmalbari[1], Abdelsamie Elobeid[2], Osama Abbadi[3]

[1]Department of biochemistry, Orotta College of Medicine and Heaalth Sciencs, Asmara, Eritrea.

[2]Department of Clinical Chemistry, Faculty of Medical Laboratory Sciences, Omdurman Islamic University, Sudan.

[3]Department of Biochemistry, Faculty of medicine, Omdurman Islamic University, Sudan.

Abstract: **COVID19 had hit the world population and health systems very hard. The current pandemic caused by this virus exposed many weak links in the health management both locally and globally. The effort on combating the disease caused by SARS-CoV-2 should not be limited to finding a cure or a vaccine; supporting managements are also beneficial in reducing the symptoms, boosting immunity, and accelerating the recovery process. In this review the authors spotted the light on some important traditional regimens, minerals, and vitamins that have eminent effects on the management of COVID19.**

Keywords: **Traditional Medicine, COVID19, Zinc, Iron, Vitamins.**

1. INTRODUCTION

Since the ancient time people use plants as a good source of nutrition as well as remedies for treatment, of many diseases. With the revolution of science, the knowledge about the medicinal plants in regard to their constituents and actions had increased significantly. Some of the principle constituent of these plants may be hazardous to man or animals. The toxicity may result either from narrow therapeutic indices of the plants or due to over dosage of these plants; this is mainly because there is no standardized dosage system in traditional medicine practice. Nowadays in many parts of the world-even in the west, plants have been considered a potential source of important alternative drugs. In Africa, Asia, and china there is an increasing interest in herbal medicine, and actually it may be the only source of health care in remote rural areas. Although a great deal of researches has been carried out over the last years in the toxicity of medicinal plants, the toxic effects of many of these plants are not yet being studied. The use of herbs to treat disease is almost universal among non – industrialized societies, and many of the pharmacological agents currently available to physicians had been used as herbal remedies, including opium, aspirin, digitalis and quinine. The world health organization estimated that 80 percent of the populations of certain Asian and African communities are depending on traditional herbal medicine **[1]**. The following popular medicinal plants: M*oringa oleifera*, A*cacia nilotica*, Zingiber officinale, cinnomomum, cipmpinella, Nigella Sativa, honey, Sudan peanut and olive oil, are used in the treatment of many disorders, and they are used in many countries including China, Sudan, and others African countries, against COVID-19 in low dosage.

2. CORONA VIRUSES (CoVs).

Belong to the subfamily Ortho-coronavirinaein; the family of Coronaviridaein; the order Nidovirales; and this subfamily includes α-coronavirus, β-coronavirus, γ-coronavirus, and ϱ-coronavirus [2]. Corona viruses are zoonotic and, in the last decades, have shown to be capable of infecting humans as well [3].The outbreak of severe acute respiratory syndrome (SARS) in 2002 and Middle East respiratory syndrome (MERS) in 2012 has demonstrated the lethality of coronaviruses when they cross the species barrier and infect humans [4]. SARS-CoV and MERS-CoV all belong to the β-corona virus family. Recently, a novel flu-like coronavirus (COVID19) related to the MERS and SARS corona viruses was found at

the end of 2019 in China in Wuhan [5], and the evidence of human to human transmission was confirmed among close contacts and contaminated with the viruses [6].The genome of COVID19 is a single-stranded positive-sense RNA[7]. The sequence analysis showed that the Covid-19 possessed a typical genome structure of corona virus and belonged to the cluster of β-corona viruses [8]. COVID19 was more than 82% identical to those of SARS-CoV [8]. COVID-19 now spread worldwide as a pandemic. Currently, there is no registered treatment or vaccine for this disease. In the absence of a specific treatment for this novel virus, there is an urgent need to find an alternative solution to prevent and control the replication and spread of the virus by lock down the country address mask make good distances.

3. PATHOPHYSIOLOGY AND PATHOGENESIS

Corona viruses are transmitted from animals to humans, and recently from human to human through respiratory droplets, cough or contaminated hands. The virus enters to GIT or lung via inhalation. This virus may stay for three days in the nasopharynx, if it's dry, after that it enter to lung cells through a tarns-membrane receptor called ACE type 2 [9]. There are two lung cells types: one is the alveolar cell which is responsible for Gas exchange, and type two is macrophage cells which produce lung surfactant and act as defense line. The virus has spike protein which acts as substrate ligand to enzyme ACE type two. This protein possesses a protease enzyme activity and it is very rich with serine. The virus causes damage to the alveolar cells type two, the macrophage try to produce cytokines like interleukin 1 and 6 and 10 and Tumor necrosis factor, and for this reason patient come with high interleukins, and these inflammatory mediators damage the alveolar cells. Vasodilatation occurs near type one alveoli, and this leads to increased capillary permeability and fluid accumulation between blood vessels and alveoli and consequently gas exchange is impaired. This later lead to short of breath, hypoxia, and hypoxemia. After the damage of type two alveoli, the surfactant is decreased and this lead to lung collapse, fluid enter to alveoli and cause edema and patient come with cough or productive cough[10]. After lung collapse and edema patient develop acute respiratory syndrome (ARS). In the CNS, When type two cells are damaged the interleukin 1 and 6 and 10 will be librated and these inflammatory mediators make the hypothalamus produce prostaglandin. This hormone converts energy into heat by increasing the metabolic rate, causing high grade fever and also can lead to brain stroke, especially among adults due the reaction of virus against immune storm. Hypoxia might stimulate peripheral chemo-receptors and this could cause tachycardia, the blood pressure will decrease which lead to decrease blood volume, then perfusion will decrease and this can lead to multisystem failure.

4. CHEMICAL CRITERIA OF THE TRADITIONAL DRUGS

In some countries in Africa the patients who infected with covid 19 they were used some medicinal plants, like*Moringa oleifera*, A*cacia nilotica* , Zingiber officinale cinnomomum, cipmpinella,andNigella Sativa. Biochemical screening showed that these plants contains:

4.1. Alkaloids.

Alkaloids are chemical polyamine compounds with heterocyclic nitrogen ring. They are produced by plants and animals and by a large variety organism including bacteria and fungi. Many alkaloids are toxic to other organisms, and used on medication like local anesthesia and Hyperion agents [11]**.** The role of alkaloids for living organism that produce them is still under question [12]. Alkaloids are known to regulate plants growth. Corona virus 19 upon entering the cell produces non structural proteins (NSPs). It is possible that polyamines react with the NSPs and prevent virus from causing respiratory illness.

4.2. Polyphenols.

Polyphenols are compounds which contain phenol rings such as thiocyantes that give grapes their purple color, and the tannins that give tea its astringency [13]. Coronaviruses are coated by phospholipids such as phosphotidyl serine, choline, inositol, sphingomylein and cholesterol. Polyphenols inhibit fats and protein formation in the cells [13].

4.3. Glycosides.

They are molecules in which a sugar is bound to a non- carbohydrate moiety, usually a small organic molecule. In animal and humans, poisons are often bound to sugar molecules as a part of their elimination process from the body, corona virus contain N-glycolicsidic bonds between the bases and sugar and hence Glycosides could bind instead thereby inhibiting the virus replication .

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4.4. Terpenes.

These are strong smelling molecules produced by a variety of plants. Teroids are derivatives of the terpenes which play role in steroid synthesis. The terpenoid, sometimes called Isoprenoid, is derived from a five – Carbone isoprene unit. Usually corona virus affects lung cells and cause edema, and edematous lung is treated by steroid. Terpenes play a role in traditional herbal remedies and are under investigation for antibacterial and other pharmaceutical function. Isoprene plays a role in vitamin A, D, E, and K biosynthesis; deficiency in vitamin D is caused death among elderly patient with corona. Steroids and sterols in animal are biologically produced from terpenoid precursors [14].

4.5. Saponins.

They are chemical compounds found in particular abundance in various plant species. Like soap, they produce foams when shaken in a solution [15]. The a-glycones (Glycoside – free) portions of saponins are termed sapogenins. Saponins may enhance nutrient absorption and aid in animal digestion. Saponins were being promoted commercially as dietary supplements and nutraceuticals. Saponins are used widely for their effect on ammonia as they inhibit urease enzyme and splits up urea in feces [16]. Overdose of saponin can lead to heamolysis, especially in Acacia nilotica [17].

4.6. Triterpenoids saponins.

Triterpenoid is a type of terpenes contain C10 (ten carbons).Cholesterol and phytosterol are triterpenes, which reduce surface tension of water through foaming [18].

4.7. Tannins.

Tannins are found in extracts of many plants and they have the ability to precipitate proteins. They are high molecular weight compounds which are used to treat diarrhea and superficial injuries. They are phenols in structure. The common one is polyphenol which not soluble in organic solvents and soluble in water. Tannins precipitates amylase enzyme which is produced from Salvia gland. Tannins are hydrolyzed to produce Gallic and Ellagic acid [19].Corona virus covid -19 move to the intestine and settles in the brush border. There is a trans-membrane receptor called ACE type two; it's a protease enzyme similar to ACE in the lungs. Both act on glycoproteins and they are similar to carboxy- peptidases. The Coronaviruses damage epithelial and endothelial cells of intestinal mucosa and cause diarrhea in 25% of cases. It might be this protein denaturing capacity of tannins that denatures the spike shape of the virus [20]. The protein denature potential of tannins is very powerful that an over- dose of tannin can damage the liver and kidneys [20].

4.8. Sterols.

Sterols- also known as steroid alcohols- are a subgroup of steroids. They occur naturally in plants, animals and fungi with the most familiar type of animal sterol being cholesterol. Cholesterol is a vital animal processor of fat- soluble vitamins and steroid hormones. Phytosterol is a sterol of plants where it serves a role similar to cholesterol in animal cells. Phytosterol have been shown in clinical trials to block cholesterol absorption sites in human's intestine, thus helping to reduce cholesterol in human [21].Therefore sterol may reduce the cholesterol content in the virus [22].

4.9. Coumarin.

Is a benzo-pyrone; a colorless crystalline with a sweet odor. Coumarin is hepatotoxic in animals models and is a precursor reagent in the synthesis of a number of synthetic anticoagulant pharmaceuticals such to dicourmarol and warfarin. It has a bitter taste and animals tend to avoid eating it. It is used in the treatment of asthma [23]**.** Coumarin is moderately toxic to the liver and kidneys, with a median lethal dose (LD 50) [23].

4.10. Coumarin and Glycosides.

Derivatives of benzo - ∝ pyrone such as coumarin (the lactone of hydroxy cinnamic acid), aesculetin, umbelliferone, and scopoletin are common in plants both in the free-state and as glycosides. Some 100 natural coumarins have been isolated. Coumarin itself has been found in about 150 species belonging to over 30 different families. This powerful anti-coagulant and hemorrhagic agent can cause the death of animals consuming the spoiled fodder [24]. Covid -19 causes pulmonary embolism, and the best treatment for this complication is heparin, and warfarin (which is derived from coumarin). The reaction between the virus and immune system lead to clotting disorders.

4.11. Flavonoids.

Flavonoids were referred to as vitamin β. Chemically, they have the general structure of 15 –carbon skeleton. Flavonoids are important plant pigments. In-vivo studies in rats have shown that Flavonoids have anti-oxidant activity [25]. Covid-19 damages lung and intestine cells, then interleukins 1, 6, and 10 (which stimulate the hypothalamus through prostaglandin to increase the metabolic rate and convert energy into heat, i.e. fever). Flavanoids act as thermogenic compounds, which accelerate our body ability to burn fat as energy, not fever, against prostaglandin [25]. Some plants such as moringa and Acacia nilotica are rich with iso-thiocyanate, which produce glycosides. This toxin may affect viral proteins. Some compounds in Moringa enhance WBCs count elevation (Covid- 19 usually lead to lymphopenia). Moringa leaves have 4 time the amount of Beta carotene than in carrots, 17 times more calcium than that of milk, 25 times more iron than that spinach and 46 antioxidant than the green leaves [26], [27]. Studies has shown that individuals with defects of vitamin D are more susceptible to death from Covid 19 and also developed to DM. Flavonoids are an important class of natural products and have several subgroups, which include chalcones, flavones, flavonols, and isoflavones. Flavonoids have many functions besides their antioxidant effects, for example, they also have antiviral abilities. Shimizu et al. [28] had found that flavonoids from *Pterogyne nitens* could inhibit the entry of the hepatitis C Virus. Jo et al. suggested that the anti-corona virus activity of some flavonoids (Herbacetin, rhoifolin and pectolinarin) was due to the inhibition of 3C-like protease (3CLpro) [29]. Other flavonoids (Herbacetin, isobavachalcone, quercetin 3-β-d-glucoside, and helichrysetin) were also found to be able to block the enzymatic activity of MERS-CoV/3CLpro [30]**,** biflavonoids from Torreya nucifera also inhibited the effect of SARS-CoV/3CL proteases.

5. THE ROLE OF VITAMINS IN COVID-19

5.1. Vitamin D.

A high number of healthy adults were reported to have low levels of vitamin D, mostly at the end of the winter season [30]. In addition, people who are house-bound or institutionalized and those who work at night may have vitamin D deficiency, as do many elderly people, who have limited exposure to sunlight [31]. The COVID19 was first identified in winter of 2019 and mostly affected middle-aged to elderly people. The virus-infected people might have insufficient vitamin D. In addition, the decreased vitamin D status in calves had been reported to cause the infection of bovine coronavirus [32], therefore; vitamin D could work as another therapeutic option for the treatment of this novel virus.

5.2. B vitamins.

B vitamins are water-soluble vitamins and work as coenzymes. Each B vitamin has its special functions, for example, vitamin B2 (riboflavin) plays a role in the energy metabolism of all cells. Vitamin B2 deficiency had been suspected to occur among elderly U.S.A citizens [33]. It had been reported that vitamin B2 and Ultraviolet light effectively reduced the titer of MERS-CoV in human plasma Products. Vitamin B3, also called nicotinamide, enhances killing of Staphylococcus aureus through a myeloid-specific transcription factor and vitamin B3 was efficacious in both prophylactic and therapeutic settings [34], moreover, vitamin B3 treatment significantly inhibited neutrophil infiltration into the lungs with a strong anti-inflammatory effect during ventilator-induced lung injury. However, it also paradoxically led to the development of significant hypoxemia [34]. Vitamin B6 is also needed in protein metabolism and it participates in over 100 reactions in body tissues. In addition, it plays important role in body immune function as well. As shortage of B vitamins may weaken host immune response, they should be supplemented to the virus-infected patients to enhance their immune system, therefore, B vitamins could be chosen as a basic option for the treatment of COVID19.

5.3. Vitamin C.

Three enzymes participate in collagen hydroxylation. These reactions add hydroxyl groups to the amino acids proline or lysine in the collagen molecule via prolyl hydroxylase and lysyl hydroxylase, both requiring vitamin C as a cofactor [35]. Hydroxylation allows the collagen molecule to assume its triple helix structure and making vitamin C essential to the development and maintenance of scar tissue, blood vessels, and cartilage and bone. Vitamin C also is well known for its antioxidant activity (radical damage DNA in germ cell and in somatic cell can lead to mutation and cancer). It acts with super oxide &hydroxyl to yield mono-dehydro-ascorbate and hydrogen peroxide or water. Moreover, vitamin C supports immune functions and protects against infection caused by a coronavirus [36]. Atherton et al. [37]reported that vitamin C increased the resistance of chick embryo tracheal organ cultures to avian corona virus infection. Vitamin C deficiency is

detrimental to immune function, resulting in reduced resistance to pathogens [38]. The COVID19 had been reported to cause lower respiratory tract infection, so vitamin C could be one of the effective choices for the treatment of COVID19.

5.4. Vitamin E.

Vitamin E is a lipid-soluble vitamin and it includes both tocopherols and tocotrienols [39]. Vitamin E plays an important role in reducing oxidative stress through binding to free radicals as an antioxidant [14]. Vitamin E deficiency had been reported to intensify the myocardial injury of coxsackie virus B3 (a kind of RNA viruses) infection in mice and increased the virulence of coxsackie virus B3 in mice due to vitamin E or selenium deficiency [16]. In addition, the decreased vitamin E and D status in calves also indirectly caused the infection of bovine coronavirus [32]**.**

6. OMEGA - 3 POLYUNSATURATED FATTY ACIDS

Among the fatty acids, it is the ω-3 PUFAs which possess the most potent immune modulating activities, and among the ω-3 PUFA, those from fish oil—EPA and DHA—are more biologically potent than ALA.

Some of the effects of omega-3PUFA are brought about by modulation of the amount and types of eicosanoids made. Other effects are elicited by eicosanoid-independent mechanisms, including actions upon intracellular signaling pathways, transcription factor activity and gene expression. Chain polyunsaturated fatty acids (PUFAs) are important mediators of inflammation and adaptive immune responses [40]. Omega-3 and omega-6 PUFAs predominantly promote anti-inflammatory and pro-inflammatory effects. They are precursors of resolvins/protectins and prostaglandins/leukotrienes, respectively [40]. Begin et al. [41] had studied plasma lipids levels in patients with AIDS and had found that there is a selective and specific lack of the long- chain PUFAs of omega-3series, which are found in high concentrations in fish oils. In addition, protection D1, the omega-3 PUFA-derived lipid mediator could markedly attenuate influenza virus replication via RNA export machinery. Add to that, the treatment of protectin D1 with peramivir could completely rescue mice from flu mortality [42]. Leu et al. [43] found that several PUFAs also have anti-hepatitis C virus (HCV) activities, therefore, Omega-3 including protection D1, which served as a novel antiviral drug, could be considered for one of the potential interventions for COVID19 management.

7. SUDAN PEANUT

It's very rich with Derivatives of arachidonic acid. This fatty acid produces Prostanoids, prostaglandins (PG), Prostacyclines (PGI2), and Thromboxanes (TX). All these compounds act in the immune system, as well as Leukotriens & Lipoxins. Thromboxanes are usually produced by platelets. Leukotriens, first found in leukocytes (WBC) are Inflammation mediators which facilitates chemotaxis, help immune cytokine upgrade, and increase capillary permeability [44].

8. SELENIUM

Selenium is an essential trace element for mammalian redox biology [35]. The nutritional status of the host plays a very important role in the defense against infectious diseases [36]. Nutritional deficiency impacts not only in the immune response but also the viral pathogen itself. Dietary selenium deficiency that causes oxidative stress in the host can alter a viral genome so that a normally benign or mildly pathogenic virus can become highly virulent in the deficient host under oxidative stress [45]. Deficiency in selenium also induces rapid mutation of benign variants of RNA viruses to virulence [45]. It had been reported that selenium deficiency could increase the pathology of an influenza virus infection and also drive changes in genome of coxsackie virus, permitting an a-virulent virus to acquire virulence due to genetic mutation [46], [47]. Selenium can assist a group of enzymes that, in concert with vitamin E, work to prevent the formation of free radicals and prevent oxidative damage to cells and tissues [48]. It was reported that synergistic effect of selenium with ginseng stem-leaf saponins could induce immune response to a live bivalent infectious bronchitis corona virus vaccine in chickens [49]. Therefore, selenium supplementation could be an effective choice for the treatment of COVID19.

9. IRON

Iron is important for both host and pathogen. Iron deficiency can impair host immunity, while iron overload can cause oxidative stress to propagate harmful viral mutations [50]. Iron deficiencies have been reported as a risk factor for the development of recurrent acute respiratory tract infections [51].

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10. NIGELLA SATIVA (NS).

The beneficial impacts of NS oil on the immune status of COVID-19 patients include enhancement of the NK cell count and increase CD8 counts [52]. Percentage of lymphocytes, were confirmed to rise [53].

11. HONEY

The biological value of honey is determined by a series of beneficial effects. Honey sugars are more easily assimilated by the human body. Phosphates content of honey helps to make good use of glucose. Also, vitamins contained in honey-although at a low concentration, ensures the absorption and utilization of sugars [54]. It contains significant amounts of minerals and trace elements essential for humans. The content varies greatly among the different types of honey, indeed, at least for zinc, it has been proven that honey is found in the most readily assailable form of the human organism and in quantities capable of greatly contributing to the satisfaction of daily needs of a man. In general, potassium, selenium and chromium are fairly available in honey [55], [56]. Honey contains calcium, iron, magnesium, phosphorus, vitamins B1, B2 and a list of enzymes. These components of the honey give it highly remarkable medical properties [57]. Honey is tonic as it increases heart rate, also it reduces stomach ulcer problems, relieves insomnia, constipation, sore throats, and respiratory diseases and generally contributes to good functioning of the body [58]. Nowadays honey is widely used against Covid-19 with other traditional herbs, and many patients had been recovered. Honey consumption helps in quicker recovery of health in cases of anemia due to the iron it contents, and COVID19 is known to cause anemia. It is often used in cases of intoxication because it helps to accelerate the metabolism as obvious by its ability to heal wounds a1nd burns. In traditional medicine, it is used as a stimulant, tonic and anti-pruritic against anorexia and malaise, it helps in relieving tiredness, coughing and colds, and finally it facilitates sleep in ill insomniac patients.

12. ZINC

Zinc is a dietary trace mineral and is important for the maintenance and development of immune cells of both the innate and adaptive immune system [59]. Zinc deficiency results in dysfunction of both humoral and cell mediated immunity and increases susceptibility to infectious diseases [60]. Zinc supplement given to zinc-deficient children reduces measles-related morbidity and mortality caused by lower respiratory tract infections [61]. Increasing the concentration of intracellular zinc with zinc ionophores such as pyrithione can efficiently impair the replication of a variety of RNA viruses [62]. In addition, the combination of zinc and pyrithione at low concentrations inhibits the replication of SARS coronavirus (SARS-CoV) [62], therefore, zinc supplements may have effect not only on COVID19-related symptoms like diarrhea and lower respiratory tract infection, but also on COVID19 itself. In cell culture studies, high Zn2+ concentrations and the addition of compounds that stimulate cellular import of Zn2+ , such as hinokitol (HK), pyrrolidine dithiocarbamate (PDTC) and pyrithione (PT), were found to inhibit the replication of various RNA viruses, including influenza virus [63], respiratory syncytial virus [64], and several picornaviruses [65], [66], [67], [68]**.** In vitro studies with purified rhinovirus and poliovirus 3C proteases revealed that protease activity was inhibited by Zn2**+ [**63]**.** Moreover, an inhibitory effect of Zn2+ was reported on the activity of purified RdRps from rhinoviruses. Another study mentioned that the zinc-ionophore pyrithione (PT), in combination with Zn2+, was a potent inhibitor of the replication of SARS-coronavirus (SARS-CoV) RNA-dependent RNA polymerase.

❖ **Zinc sulphate.**

Zinc is known to be essential for the body. It's a component of insulin and many enzymes including carbonic anhydrase (which transport C02 from RBCs to the lungs)help respiration, ACE type 2 in the intestine and lungs (macrophage cells support and immune), and Carboxypeptidase, a necessary enzyme for peptide digestion. Zinc sulphate is used to treat diarrhea in bacterial or viral infections [60] where sulphate has a protective role in epithelium and endothelium of mucosa. Over the last 10 years zinc sulphate was used in treatment severe diarrhea in the subsequent months, znic has been proven to reduce mortality in the management of children with severe malnutrition. In the lungs, nasal znic sulphate drops prevent pneumonia and virus reinjection. Znic sulphate is an alkylating agent, i.e. it alkylate the keto-group in position 6 of guanine(G) and in number 4-of thymine (T) so that base analog base paring affinity is altered and transcription (or replication) mutation result. Zinc sulphate usullay binds with G or T and prevent virus replication thereby stops the diarrhea.

Important points concerning Zinc:

- Zinc sulphate (inhibit replication of corona virus by binding of phosphate group of virus to zinc iono-statistic bond) and also bind with guanine
- Zinc sulphate(accelerate immune system) 20mg children 50mg adults increase dose patients with Diabetes and patients on dialysis
- Zinc sulphate reduced mortality from pneumonia (secondary infection of corona virus)
- Zinc sulphate nasal spray for three days prevent corona virus re infection
- Zinc sulphate has role in decrease lipoprotein (micelle) corona virus like micelle zinc has hypo-lipidemic effect
- Zinc sulphate and oral rehydration –life saving in malnutrition (give to children as preventive)
- Zinc sulphate with Remedivir the recovery will be high in corona virus COVID19.

13. CONCLUSION

The use of traditional medicine and supportive therapy in COVID-19 battle proved efficient in managing the symptoms, boosting immunity, and improving the general conditions of the patients. A great advantage of the traditional medicine is their absence of undesirable side effects and toxic threat. Authors recommend the use of the abovementioned remedies as a prophylaxis in healthy individuals, particularly people of high risk of contaminations, in COVID positive patients, and also in recovered COVID-19 survivors.

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