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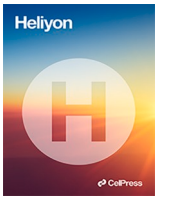

Review article

Promising role of Vitamin D and plant metabolites against COVID-19: Clinical trials review

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ABSTRACT

Vitamin D possesses immunomodulatory qualities and is protective against respiratory infections. Additionally, it strengthens adaptive and cellular immunity and boosts the expression of genes involved in oxidation. Experts suggested taking vitamin D supplements to avoid and treat viral infection and also COVID-19, on the other hand, since the beginning of time, the use of plants as medicines have been vital to human wellbeing. The WHO estimates that 80 % of people worldwide use plants or herbs for therapeutic purposes. Secondary metabolites from medicinal plants are thought to be useful in lowering infections from pathogenic microorganisms due to their ability to inhibit viral protein and enzyme activity by binding with them. As a result, this manuscript seeks to describe the role of vitamin D and probable plant metabolites that have antiviral activities and may be complementary to the alternative strategy against COVID-19 in a single manuscript through reviewing various case studies.

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1. Introduction

COVID-19, also known as 2019 novel coronavirus (2019-nCoV), is a respiratory illness. The first Covid-19 case was found in Wuhan, the provincial capital of Hubei, China, and it rapidly spread over 215 other countries [1,2]. So far, 7 different varieties have been identified, including HCoV-OC43, HCoV-229E, HCoV HKU1, HCoV NL63, Middle East respiratory sickness (MERS-CoV), and 2019's novel coronavirus (nCoV) [3]. Covid-19 was the third illness pandemic of the corona virus family in the human population throughout the 21st century, behind SARS-CoV in 2002 and MERS-CoV in 2012 [4–6]. The severe acute respiratory syndrome (SARS) outbreak that occurred in 2003 in Guangdong (China) [7,8] infected 8000 persons and caused 800 fatalities in 26 countries. Only ten years later, MERS, another catastrophic coronavirus outbreak that infected more than 2000 people and took 858 lives worldwide, struck the world [9,10]. However, the COVID-19 pandemic brought on by the SARS CoV-2 virus led to extraordinarily high rates of illness and death worldwide. COVID-19 was classified as a Public Health Emergency of International Concern by the World Health

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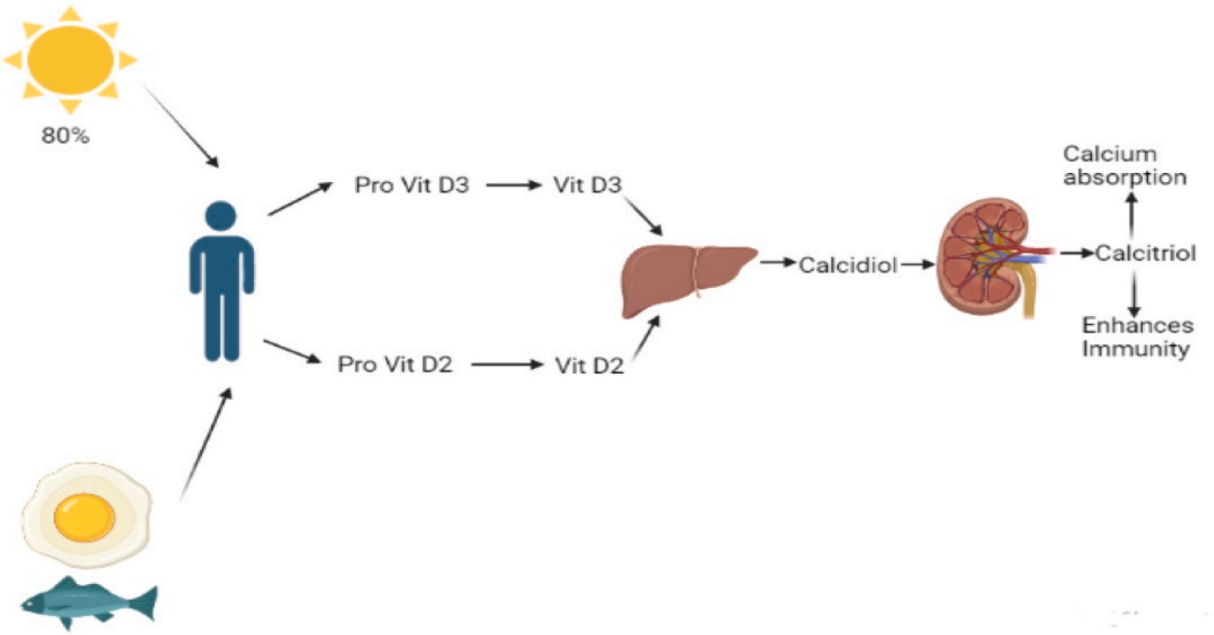

Fig. 1. Vitamin D synthesis and its advantages.

Organization (WHO) on January 30, 2020 (https://www.who.int/) [7].

In a systematic literature review and meta analysis by Zheng and his co-worker, the patients who were male, above 65 years of age and had comorbidities such as diabetes, hypertension, and cardiovascular disease were at a greater risk factors for COVID-19 [11]. The majority of these comorbidities are linked to an unhealthy lifestyle and diet which is frequently characterised by a high consumption of processed food, saturated fats, salt, sugars and refined grains [12,13]. Nutrients are essential for growth, development, and adequate physiological functioning of one being [13]. The association between nutrition and immune system performance is currently being researched. A key immuno-nutrient that can be gained by diet in particular is vitamin D, which is however created primarily (80 %) endogenously by exposure to UV-B rays in the skin [14]. Vitamin plays a role in calcium homeostasis but it also has an immuno-modulatory properties and is protective against respiratory infections [15] (Fig. 1). Worldwide, vitamin D deficiency is regarded as a public health issue and is believed that 1 billion people are vitamin D deficient, and this affects about 50 % of the population [16]. Additionally, it improves cellular immunity, modifies adaptive immunity, and increases expression of genes related to oxidation [17]. As a result, a number of experts suggested using Vitamin D supplements to prevent and treat COVID-19.

On the other hand, since ancient times, the use of plants as medicines has been vital to human welfare [18,19]. Around 80 % of people around the world, according to the WHO, rely on plants or herbs for therapeutic purposes [20,21]. Numerous research have utilised a sizable amount of antiviral chemicals derived from a variety of plants [22–24]. Since the beginning of time, people all over the world have used plants as medicines, particularly from Asian countries as well as some African countries [25]. These plants are commonly used in folklore by tribal people due to their widespread availability and affordable cost [26]. Due to their capacity to halt viral protein and enzymatic activities by binding with them, medicinal plants' secondary metabolites are considered to be effective in reducing infections from pathogenic microorganisms [26]. The history of traditional Chinese medicine (TCM) is extensive, and has a long history of successfully treating and controlling communicable diseases. Ayurveda, which has Indian origin, is another conventional medicinal philosophy. Ayurveda offers a variety of therapeutic approaches for respiratory conditions, including steam inhalation, immunomodulators, herbal infusions, and gargling hot water, which was also encouraged in the midst of the pandemic [27]. Researchers from all over the world are screening therapeutic medications from already-existing antiviral plant secondary metabolites (PSMs) and looking for novel molecules from medicinal plantsto treat COVID-19 [28].

Taking into account of the impact of the COVID-19 risk that potentially results from low vitamin D status, we have reported various case studies to draw the correlation between low vitamin D status and COVID-19 risk. Further, we have also reported clinical studies with completed status that are investigating the efficacy and safety of traditional medicines against SARS-CoV-2. Therefore, the current manuscript aims to describe the role of vitamin D and potential plants secondary metabolites that might be used as an alternative approach against COVID-19 in a single manuscript.

1.1. COVID-19

The family of enveloped viruses known as coronaviruses (CoV) has non-segmented, positive-stranded genomic RNA [29,30]. This family of viruses known as coronaviruses can be found in both humans and animals. The genetic material that makes up the virus's core

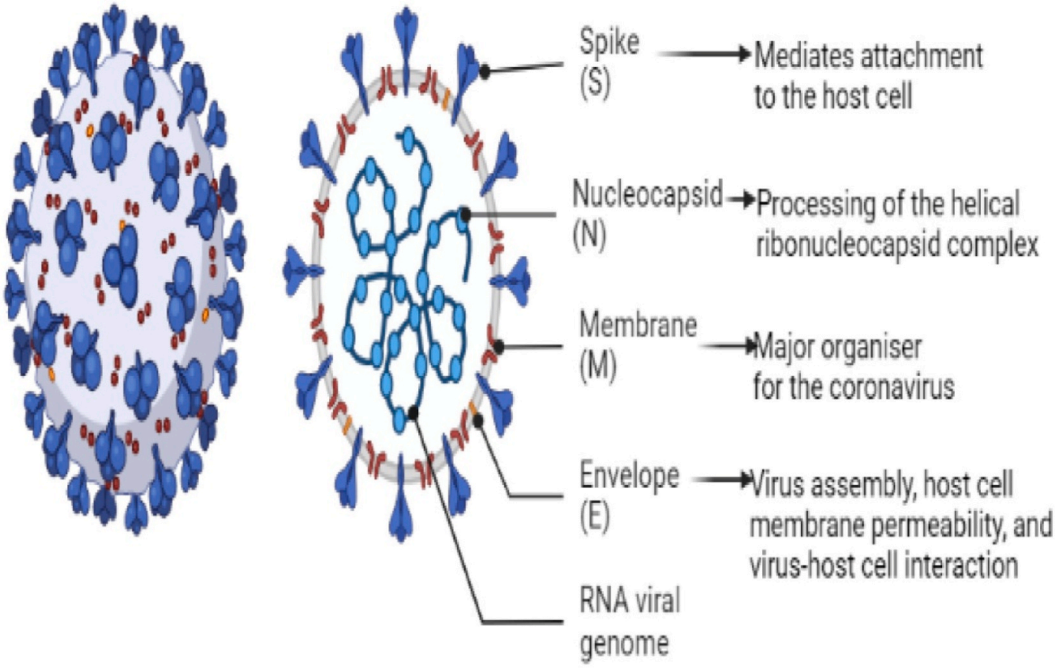

Fig. 2. Structural proteins of SARS-CoV-2 and their functions.

and the protein crown that covers its outside are its two layers of structural makeup [31]. The single-stranded RNA genome of the pleomorphic or spherical SARS CoV-2 is 26.4–31.7 kb in length, and has a crown-like glycoprotein present on its surface [32–36]. It is different from both the MERS Coronavirus and SARS-CoV despite belonging to the same family as beta-Coronaviruses (MERS CoV). According to other research, SARS-CoV-2 genes and SARS-CoVgenes have about 80 % nucleotide identity and 89.10 % nucleotide similarity [37].

When compared to the RNA genomes of other RNA viruses, CoV-2's RNA genome is one of the largest (27 kb–32kb) [38,39]. The open reading frames (ORFs) encode 4 structural proteins: the envelope glycoprotein or spike protein (S), envelope (E) protein, membrane (M) protein, and nucleocapsid (N) protein. The largest open reading frame, ORF1ab, encodes non-structural proteins. The E protein is involved in virus assembly, host cell membrane permeability, and virus-host cell interaction, the S protein mediates attachment to the host cell. The nucleocapsid (N) protein is often involved in the processing of the helical ribonucleocapsid complex, which also includes certain accessory proteins. The M protein is known as a major organiser for the coronavirus assembly (Fig. 2) [32, 40]. The SARS CoV-2 genome contains six different types of mutations, with three described in the *orf 1 ab* gene, two in the S gene, and the final one in the *orf 7b* and *orf 8* genes [41,42].

Three stages of the SARS-CoV-2 virus infection can be distinguished: the asymptomatic phase, the non-severe symptomatic phase, and the severe infection stage [43]. According to reports, SARS CoV-2 patients have high levels of cytokines and chemokines; these levels are particularly elevated in patients who are admitted to intensive care units (ICUs) [44,45]. A patient enters a critical stage as a result of these noticeably high levels. SARS CoV-2 enters the body of the host via eyes, nose and mouth and, in order to complete its life cycle, binds to the receptor-binding domain (RBD) using the surface glycoprotein (Spike-protein) of the virion that seeks to engage with the hACE2 receptor [46,47]. Cellular transmembrane serine protease 2 (TMPRSS2) and furin, coupled with the viral receptor ACE2, are necessary for the SARS CoV-2 entrance mechanism [48,49]. The virus's envelope and capsid, however, are lost when the virion particle fuses with the host cell membrane. In order to translate ORF1a and ORF1ab into pp1a and pp1b polypeptides, the virus distributes its genetic material (RNA) into the host cell's cytoplasm [35,50]. These polypeptides are then divided into 16 non-structural proteins (NSPs), which are in charge of transcription and replication, by the chymotrypsin-like protease ($3CL^{pro}$) [51]. Cells that have been infected go on to create proteins after being taken over by SARS CoV-2. In this instance, SARS CoV-2 assembly into fresh copies of virion particles is supported by the immune system [52,53] as vitamin D deficiency may lead to immune dysfunction, reduce pro-inflammatory cytokines and increase anti-inflammatory cytokines and disseminated intravascular coagulation in COVID-19 patients [54]. Newly produced viral nucleic acids and proteins exocytose out of the cells after forming in the lumen of the Endoplasmic Reticulum Golgi Intermediate Compartment (ERGIC) (Chen, Liu et al., 2020; Kim, Lee et al., 2020). Viroids produced by infected human cells spread infection to uninfected human cells.

1.2. Vitamin D

Vitamin D, commonly known as cholecalciferol (vitamin D3) or ergocalciferol (vitamin D2), is a steroid prohormone and a

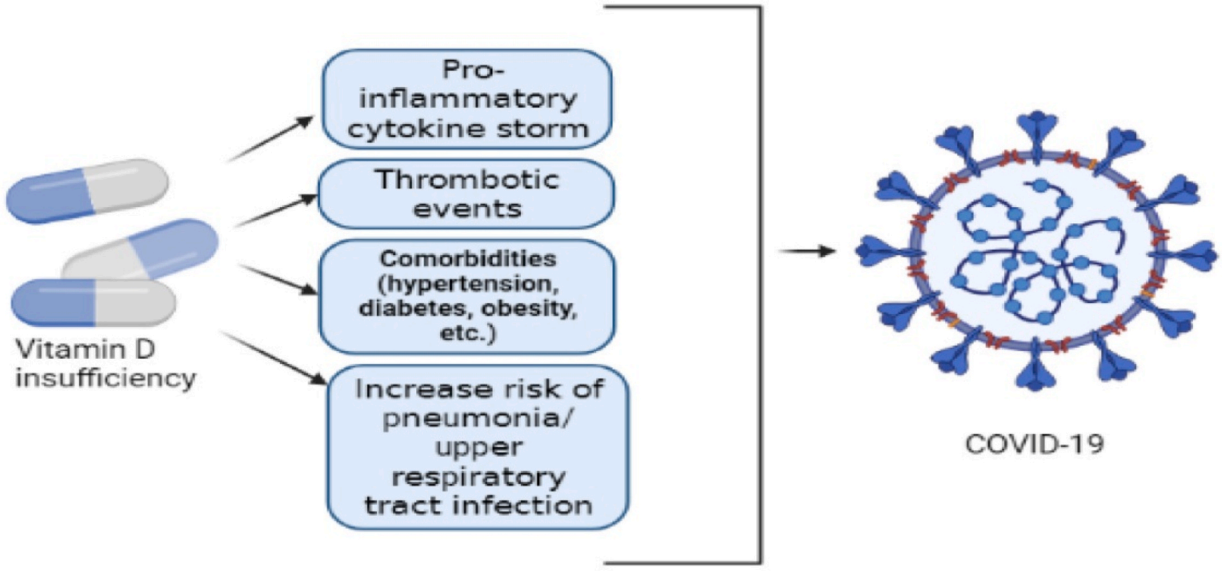

Fig. 3. Risk factors associated with Vitamin D insufficiency leading to increased susceptibility to COVID-19.

necessary lipid-soluble vitamin. Although, vitamin have been postulated to possess functions such as, extra-skeletal effects, particularly on the immune system, and modulation of the immune response in both infectious and autoimmune diseases, the advantages of vitamin D go far beyond the regulation of calcium and phosphorus metabolism and the maintenance of bone health [55–57]. Since very few foods contain vitamin D, the principal source of vitamin D is UV-B radiation of 7-dehydrocholesterol on bare skin exposed to strong sunshine [58]. The action of vitamin D is due to its 125-dihydroxy form. However, extra-renal vitamin D metabolism and its regulatory loop are still poorly understood [59]. Various evidence suggests that local synthesis of active vitamin D is essential for the immunomodulatory role of vitamin D against inflammation and microbes beyond the systemic level of 25-hydroxyvitamin D and bone. It is now widely accepted that vitamin D reduces immunological activation mediated by monocytes and cells, which in turn reduces the production of antibodies, cytokines, and lymphocyte proliferation [60].

1.3. The relevance of vitamin D to COVID-19

High levels of pro-inflammatory cytokines and an elevated risk of pneumonia and viral upper respiratory tract infections have both been linked to vitamin D insufficiency. Acute respiratory distress syndrome (ARDS), a significant driver of the severity of sickness in COVID-19 patients, is also a risk factor for it. Infected patients frequently experience increased thrombotic events, which are also linked to vitamin D insufficiency [61,62]. Patients with chronic illnesses like hypertension, gastroenterological disease, and diabetes as well as individuals in the elderly age group, those who are obese and smoke frequently have low vitamin D levels (Fig. 3). Additionally, it has been noted that COVID-19 is more common and has more serious problems in these individuals. According to a multitude of literature sources, vitamin D deficiency is common in India, the Middle East, South America, Africa, and Australia [63–65]. It may be a significant risk factor for COVID-19 based on the observation that the group of patients with vitamin D deficiency also suffer more complications and higher mortality from COVID-19. Patients with a fat malabsorption syndrome and bariatric patients typically are unable to absorb the fat-soluble vitamin, and patients with nephritic syndrome also loses 25(OH)D bound to the Vitamin D binding protein in the urine [63].

1.4. Association of vitamin D with COVID-19: case studies

The study conducted by Jain and group in 2020 [66] in India at M.L.B Medical college, Jhansi to analyze the vitamin D level in COVID-19 patients and its impact on disease severity as continuous prospective observational study period of six weeks. Patients with COVID-19 who were asymptomatic (Group A) or who were critically ill and required ICU hospitalisation were included in the study (Group B). Measurements of 25(OH)D serum levels were made. 154 patients totalled for the study, with 91 in Group A and 63 in Group B. The difference in the mean vitamin D levels in Groups A and B were 27.89 ± 6.21 ng/mL and 14.35 ± 5.79 ng/mL, respectively was extremely significant. In Group A and Group B, the prevalence of vitamin D insufficiency was 32.96 % and 96.82 %, respectively. 90 patients out of 154 total patients were determined to be vitamin D deficient (Group A: 29; Group B: 61). Vitamin D deficiency had a higher fatality rate (21 % vs. 3.1 %). Patients with severe COVID-19 have notably low levels of vitamin D. All of this result in a higher mortality rate for COVID-19 patients who are vitamin D deficient (Table 1).

In another Indian data, a hospital-based cross-sectional study was carried out to determine the vitamin D status among COVID-19 patients in a tertiary care hospital in Patna, Bihar. However, in this case, demographic and co-morbidity data were also considered. In

Table 1
Case study: Vitamin D insufficiency associated with COVID-19 risk (Jain et al., 2020).

S.No.		Group A	Group B
1.	Condition	Asymptomatic	Critically ill (requires ICU)
2.	Number of patients	91	63
3.	Mean vitamin D level difference	27.89 ± 6.21 ng/mL	14.35 ± 5.79 ng/mL
4.	prevalence of vitamin D insufficiency	32.96 %	96.82 %
5.	Fatality rate	3.1 %	21 %

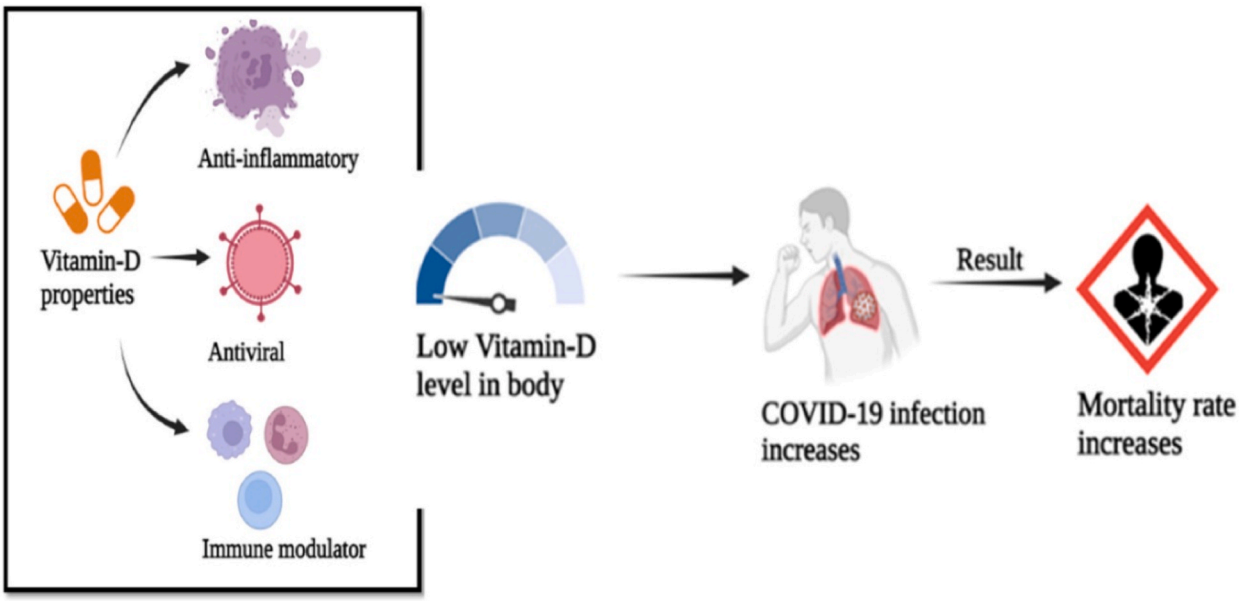

Fig. 4. Low Level of Vitamin D leads to increase risk in COVID-19 infection resulting in higher mortality rate as reported by Padhi et al., 2020.

the analysis, distinct groups of COVID-19 patients' levels of deficit and insufficiency were compared. 42.31 % of the 156 participants in the study were obese, and 17.31 % were classified as having severe clinical severity. There were 58.97 % and 89.1 % of those who were vitamin D deficient and inadequate, respectively. Male patients (61.02 %), overweight (65.52 %), and severely ill (62.96 %) were shown to have a significant prevalence. Older age is associated with greater severity ($p < 0.05$). They came to the conclusion that it is possible to gauge a patient's prognosis for COIVD-19 and alter the treatment plan based on their vitamin D levels. The course and severity of COVID-19 can be changed by using vitamin D in the proper therapeutic or preventive manner [67].

Data on SARS-CoV-2 infection and death were retrieved from the official website of the Government of India (accessed on August 16, 2020) by Padhi and her group [68]. In order to determine the average levels of 25-hydroxyvitamin D [25(OH)D] in the various parts of India, various literature databases including PubMed and Google Scholar were searched. Pearson correlation was then used to search into any potential relationships between mean 25(OH)D levels and SARS-CoV-2 infection and mortality per million of the population. The prevalence of SARS-CoV-2 infection and mortality were found to be inversely correlated ($r = 0.43$, $p = 0.02$) with the mean amount of 25(OH)D. According to the observational research, vitamin D is linked to SARS-CoV-2 infection and related mortality (Fig. 4).

A quasi-experimental study was done in France by Anneweiler and group to see if bolus vitamin D3 supplementation given during or right before COVID-19 was useful in increasing survival among frail elderly nursing care residents who had COVID-19. In this quasi-experimental study, 66 COVID-19 patients from a French nursing home were enrolled. The "Comparator group" comprised all other participants, whereas the "Intervention group" comprised those who had received bolus vitamin D3 supplementation during COVID-19 or in the month prior. Mortality according to the COVID-19 and the acute phase Ordinal Scale for Clinical Improvement (OSCI) score were the primary and secondary endpoints, respectively. Potential confounders included age, gender, daily drug intake, functional status, albuminemia, usage of corticosteroids, hydroxychloroquine, and/or antibiotics (such as azithromycin or rovamycin), as well as COVID-19 hospitalisation. At baseline, the COVID-19 severity and the usage of specific COVID-19 medications were comparable across the Intervention ($n = 57$; mean SD, 87.7 ± 9.3years; 79 % women) and Comparator ($n = 9$; mean, 87.4 ± 7.2years; 67% women) groups. A mean follow-up period of 17 days was used. 82.5 % of participants in the Intervention group and 44.4 % of those in the Comparator group in COVID-19 survived, respectively ($P = 0.023$). Vitamin D3 supplementation was associated with a full-adjusted hazard ratio for mortality of 0.11 (95 % CI:0.03; 0.48), $P = 0.003$. Compared to the Comparator group, the Intervention group had a longer survival time, according to Kaplan-Meier distributions (log-rank $P = 0.002$). The OSCI score for COVID-19 was

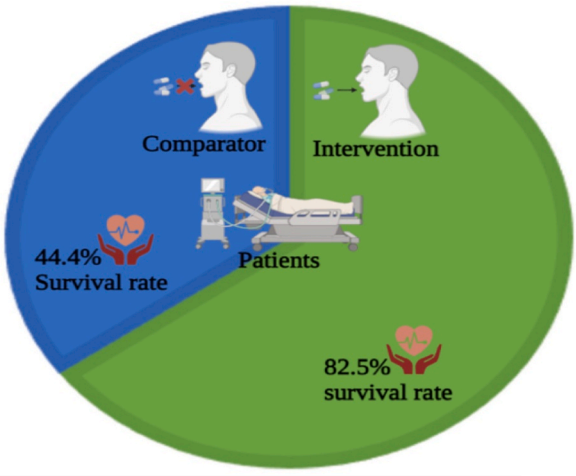

Fig. 5. COVID-19 survival rate of Comparator and Intervention group (Annweiler et al., 2020).

adversely correlated with vitamin D3 supplementation (=-3.84 [95%CI: 6.07;-1.62], P = 0.001). In conclusion, bolus vitamin D3 administration during or right before COVID-19 was linked to less severe COVID-19 and a higher survival rate in elderly fragile patients [69] (Fig. 5).

The objective of this 2020 study by Merzon and colleagues from Tel Aviv, Israel, was to assess correlations between plasma 25(OH) D levels and the probability of coronavirus disease 2019 (COVID-19) infection and hospitalisation. The 14,000 Leumit Health Services members who had at least one prior blood test for plasma 25(OH) D levels and who were tested for COVID-19 infection between February 1 and April 30 of 2020 made up the study population. A plasma 25(OH)D level that is "suboptimal" or "low" was described as one with a concentration of 25(OH)D below 30 ng/mL 782 (10.12 %) out of 7807 people tested positive for COVID-19, whereas 7025 (89.98 %) tested negative. In those who tested positive for COVID-19 compared to those who tested negative, the mean plasma vitamin D level was considerably lower (19.00 ng/mL (95 % confidence interval (CI) 18.41–19.59) vs. 20.55 (95 % CI: 20.32–20.78)). Low plasma 25(OH)D levels were linked to an elevated risk of COVID-19 infection (crude odds ratio (OR) of 1.58 (95 % CI: 1.24–2.01, P 0.001) and SARS-CoV-2 hospitalisation (crude OR of 2.09 (95 % CI: 1.01–4.30, P 0.05), according to a univariate analysis. The adjusted odds ratios of COVID-19 infection (1.45 (95 % CI: 1.08–1.95, P 0.001)) and SARS-CoV-2 hospitalisation (1.95 (95 % CI: 0.98–4.845, P = 0.061)) were maintained in multivariate models that controlled for demographic factors, psychiatric disorders, and somatic diseases. Age over 50 was strongly linked with the probability of COVID-19 infection and the chance of hospitalisation owing to COVID-19 in the multivariate analysis, as were male gender, low-medium socioeconomic position, and age over 50. They came to the conclusion that COVID-19 infection and hospitalisation seem to be independently risk factors for low plasma 25(OH)D levels [70].

Another study was carried out in the same year, 2020 to see if the COVID-19 test findings were influenced by the patient's last vitamin D level before to testing at the University of Chicago Medicine (UCM) in Chicago, Illinois using data from the electronic health record. Patients who had their 25-hydroxycholecalciferol or 1,25-dihydroxycholecalciferol levels checked within the previous year before being tested for COVID-19 between March 3 and April 10, 2020, were included in this retrospective cohort study. A total of 489 patients had their vitamin D levels checked the year before COVID-19 testing (mean [SD] age, 49.2 [18.4] years; 366 [75 %] women; and 331 [68 %] race other than White). Before undergoing the COVID-19 test, the vitamin D status of 124 subjects was classified as likely deficient (25 %), likely sufficient for 287 (59 %), and unsure for 78 (16 %). In all, 71 subjects (15 %) had COVID-19 positive test results. Testing positive for COVID-19 was linked in a multivariate analysis to advancing age up to age 50 (related risk, 1.06; 95 % CI, 1.01–1.09; P = 0.02), non-White race (relative risk, 2.54; 95 % CI, 1.26–5.12; P = 0.009), and possibly inadequate vitamin D status (relative risk, 1.77; 95 % CI, 1.12–2.81; P = 0.02) In the inadequate group, predicted COVID-19 rates were 21.6 % (95 % CI, 14.0%–29.2 %), compared to 12.2 % (95 % CI, 8.9%–15.4 %) in the sufficient group [71].

Liu et al., 2020(China) performed a comprehensive review and meta-analysis to examine the relationship between low vitamin D status and COVID-19. A thorough search was done using PubMed, Embase, and the Cochrane Library from the beginning of the database's existence until September 25, 2020. To estimate the combined data, the standardised mean difference (SMD) or odds ratio (OR) and accompanying 95 % confidence interval (CI) were used. The meta-analysis utilised random- or fixed-effect models based on heterogeneity. For the meta-analysis, ten articles totalling 361,934 participants were chosen. Overall, vitamin D deficiency or insufficiency was linked to a higher risk of COVID-19, according to the pooled OR in the fixed-effect model (OR = 1.43, 95 % CI 1.00–2.05). Furthermore, those who tested positive for COVID-19 had lower vitamin D levels than those who tested negative for COVID-19 (SMD = −0.37, 95 % CI = −0.52 to −0.21). There was a lot of heterogeneity in both endpoints. An increased risk of COVID-19 infection may be linked to low vitamin D levels, according to this systematic review and meta-analysis [72].

Surprisingly, in a study by Hastie and colleagues (2020) in Glasgow, U.K. [73], identical research was undertaken, but their subjects included black and ethnic minorities because COVID-19 and low vitamin D levels appear to disproportionately impact black and ethnic minorities. They sought to determine whether blood 25(OH)D) concentration was related to COVID-19 risk and whether it contributed

Table 2
List of some medicinal plants showing Antiviral activity.

Plant	Virus	Plant Extract/active compound used	Mode of action	Reference
Angelica dahurica, Curcuma longa, Pinus densiflora (combined extract)	influenza A virus, SARS-CoV	DMSO extract	Unknown	[77]
Cryptolepis sanguinolenta	HIV-1 PV	Ethanol and DMSO extracts	Unknown	[78]
Psorospermum febrifugium	HIV-1 PV	Ethanol and DMSO extracts	Unknown	[78]
B. micrantha	HIV-1 PV	Ethanol and DMSO extracts	Unknown	[78]
Melissa officinalis	SARS-CoV-2, Human enterovirus (EV-A71 or EV71), HSV-1,18 CPV, 19 HBV,11,20,21 HCV11,20,21	Aqueous and methanolic extract	Inhibits HSV-1 binding to host cell, replication during the post-adsorption or inhibits main protease and spike protein of SARS-CoV-2	[79–83]
Acantho spermum sps.	HSV-1	Chloroform and hexane extracts	Chloroform extract inhibits replication and the expression of early and late viral genes. Hexane extract inhibits the immediate-early and late genes	[84]
Ammi-visnaga	Bovine Rotavirus	Methanolic extract	Unknown	[85]
Justicia secunda	HHV-1	Methanolicextract	Unknown	[86]
Echinacea purpurea	HCoV-229E, Influenza A virus	Ethanolic extract	Inhibition of HCoV-229E penetration into the cell	[87]
Tinospora cordifolia	SARS-CoV-2	In silico	Binds SARS-CoV-2 main protease (COVID-19 M^{pro}), an enzyme involved in viral replication and transcription	[88]
Garcinia mangostana	SARS-CoV-2	In silico	Dual inhibitor mechanisms against two SARS-CoV-2 proteases	[89]
Spatholobussub erectus	SARS-CoV-2, SARS-CoV-1, H5N1	Percolation extract	Inhibits viral entry, blocks both SARS-CoV-2 spike glycoprotein and the host ACE2 receptor	[90]
Nigella sativa	SARS-CoV-2	Thymohydroquinone and Dithymoquinone	Unknown	[91]
Hypericum perforatum	SARS-CoV-2	Hypericin and pseudohypericin	Inhibits viral multiplication	[92]
Sambucus formosana	HCoV-NL63	Ethanolic extract	Inhibition of binding of HCoV-NL63 with Sai cell-surface receptor	[93]
Punica granatum	Influenza A virus	Ethanolic and polyphenolic extract	Inhibits viral replication, altered viral surface glycoproteins and damage to virion integrity	[94,95]
Glycyrrhiza sp.	Influenza A virus, EV71, CVA16, SARS CoV-2, NDV	Glycyrrhizin, aqueous extract	Reduction in H5N1-induced cytokine expression, H5N1-induced caspase activation & apoptosis; Suppressed EV71 & CVA16 replication, inhibition of SARS-CoV replication, adsorption & penetration	[96, 97–100]
Plantago asiatica	respiratory syncytial virus (RSV)	Aqueous extract	Inhibits RSV replication, genetranscription & protein synthesis	[101]
Clerodendrum trichotomum	respiratory syncytial virus (RSV)	Aqueous extract	Inhibits RSV replication, gene transcription & protein synthesis	[101]
Plantago major	HSV-1	Caffeic acid &chlorogenic acid	Inhibits virus replication	[102]
Cistus incanus	HIV-1	Aqueous extract	Blocked primary virus attachment to cells by selective targeting of the viral envelope glycoproteins	[103]
Clinacanthus nutans	dengue virus	Ethanolic and chlroroform extract	Inhibited dengue viral 2 in pre-entry replication step and suppressed PGE2 production	[104,105]
Picrorhiza kurroa, Ocimum tenuiflorum, Terminalia chebula	dengue virus	Aqueous	Nhibited viral attachment, inhibited helicase and protease activities	[106]
Aphloia theiformis	ZIKV	Aqueous	Inhibit viral entry	[107]
Psiloxylon mauritianum	ZIKV	Aqueous	Checks early replication of virus	[108]
Andrographis paniculata	Influenza virus	Andro-grapholide& derivatives	Blocking virus binding to cellular receptors	[109]
Curcuma longa	influenza A virus, SARS-CoV	Curcumin	Inhibition of virus-cell attachment; replication and inhibition of 3 C L protease	[110,111]
Aloe vera	Influenza virus, HSV-2	Aloin	Inhibition of viral neuraminidase activity	[112,113]
Cassine xylocarpa	HIV	Aqueous extract	Inhibits viral replication	[114]
Cyperus rotundus	HSV-1 HBV	Hydro-alcoholic extract	Inhibts viral replication	[115]
Ficus carica	HSV-1 HSV-1, ECV-11 and ADV influenza virus	Aqueous extract The hexanic and hexane-ethyl acetate from latex of fig fruit Hexanic extract	Inhibits viral multiplication	[116–118]

(*continued on next page*)

Table 2 (*continued*)

Plant	Virus	Plant Extract/active compound used	Mode of action	Reference
Magnolia officinalis	Dengue virus Type 2	Methanol extract	Reduced viral replication, reduced expression of DENV-2 nonstructural protein NS1/NS3, its replicating intermediate & double-strand RNA	[119]
Mentha pulegium	HSV-1	Methanolic extract	Unknown	[120]
Prunella vulgaris	HIV-1 Ebola virus	Aqueous extract	Inhibits early, post-virion binding events	[121,122]
Salacia reticulata	H1N1 influenza	Aqueous extract	Inhibits viral replication	[123]
Taraxacum officinale	HCV Influenza virus type A, H1N1.	Methanol extract Aqueous extract	Inhibits viral replication	[124,125]
Anthemis hyaline, Nigella sativa and *Citrus sinensis*	SARS-CoV	Ethanolic extract	Increased IL-8 level.	[126]
Artemisia annua	SARS-CoV	Ethanolic extract	Unknown	[127]
Houttuynia cordata	SARS-CoV	Aqueous extract	3CLproteaseinhibition	[128]
Rheum officinale and *Polygonum multiflorum*	SARS-CoV	Aqueous extract	InhibitstheinteractionofSARS-CoVSproteinandACE2.	[129]

to the increased incidence of COVID-19 in South Asian and African Americans. Between 2006 and 2010, UK Biobank enrolled 502,624 people, ages 37 to 73. Results of the COVID-19 test were matched to baseline exposure information, such as ethnicity and 25(OH)D concentration. For the connection between confirmed COVID-19 and 25(OH)D, as well as the association between ethnicity and both 25(OH)D and COVID-19, univariable and multivariable logistic regression analyses were conducted. For participants in the 348,598 UK Biobank, complete data were available. 449 of them had a known COVID-19 infection. Unadjusted odds ratios (OR) for vitamin D and COVID-19 infection were both 0.99 (95 % CI: 0.99–0.999; $p = 0.013$), but not 1.00 (95 % CI: 0.998–1.01; $p = 0.208$). Blacks versus whites OR = 5.32, 95 % CI = 3.68–7.70, p-value 0.001; South Asians versus whites OR = 2.65, 95 % CI = 1.65–4.25, p-value 0.001). Ethnicity was linked with COVID-19 infection invariably. The strength of the connection barely changed when 25(OH)D concentration was taken into account. Findings, however, refute any suggestion that vitamin D levels may be related to COVID-19 infection risk or that they may account for racial disparities in COVID-19 infection.

Vitamin D supplementation is a simple, inexpensive, and low-risk method that can be used to help curb the disease. Supplementing with vitamin D is extremely safe, and consuming overly high doses of vitamin D only rarely results in vitamin D toxicity. The majority of researches in kids and adults have claimed that blood levels must be higher than 150 ng/mL before there is any cause for alarm. As a result, a limit of 100 ng/mL offers a safety buffer for lowering the danger of hypercalcemia. Serum 25(OH)D concentrations in cases of vitamin D poisoning with varied toxic symptoms range from 213 to >640 ng/mL (533 to >1600 nmol/L). Testing blood calcium and 25 (OH)D levels two to four weeks after taking vitamin D is necessary to establish safety, but in most situations it is not always required. Vitamin D importance for COVID-19 patients should not be understated, and its treatment among patients can stop the progression of the illness [72].

1.5. Medicinal plants

The drug organization's global outlook has recently undergone significant change. With the ageing of the global population, the prevalence of chronic illnesses and lifestyle-related illnesses has increased, and an increasing number of people are looking to enhance their quality of life by focusing on disease prevention, the development of herbal treatments has concentrated on the treatment of cancer, ageing, chronic diseases, viral infections, and diseases linked to a certain lifestyle. Since ancient times, plants have been used as medicines and are hence crucial to human welfare [19,74]. Around 80% of people worldwide rely on medicinal plants or herbs to meet their medical needs [20]. Many researchers have made extensive use of antiviral chemicals derived from a wide variety of plants (Table 2) [23,24,75]. The use of natural alternatives to or complementary therapies has drawn more attention as a result of increased anxiety over the negative side effects of chemical drugs and the short-term efficacy of some of them. Herbal treatments are sometimes the only effective treatment available and are utilised as less harmful alternatives to conventional medications. Only a small number of plant species are investigated for their toxicity, immunity, and therapeutic potential. Consequently, there is a lot of study being done on therapeutic plants [76].

1.6. The functional role of medicinal plants to prevent SARS-CoV-2 disease

In an effort to win the war against microbial resistance, researchers are working to develop fresh and modern medications based on a variety of herbal treatments. The SARS CoV and SARS CoV-2 share a number of important traits such as they both belong to beta family, contains the same genetic material-RNA, and use the same receptor for viral attachment-ACE2, with an 86% identity and 96% similarity of genome, with almost the same pathogenesis. As a result, previously discovered antiviral plant metabolites that are effective against the SARS CoV can be thought of as COVID-19 therapeutic candidates. Additionally, researchers discovered that several proteases, including papain-like protease (PL^{pro}), main protease (M^{pro}), and RNA-dependent RNA polymerase (RdRp), are

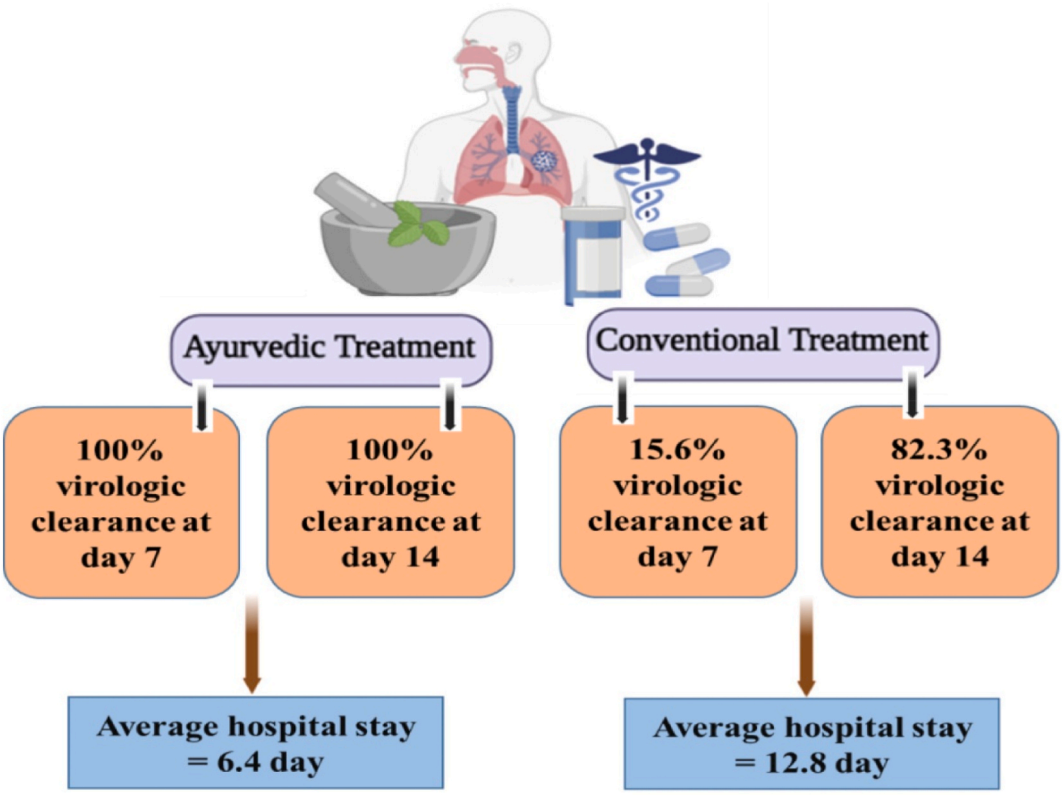

Fig. 6. Digrammatic representation of the case study of Arogyam, 2020 comparing the ayurvedic treatment with conventional treatment.

involved in the replication and maturation of Covid-19's viral nucleic acids. Because they convert viral polyproteins like pp1a and pp1ab into effector proteins, these proteases are thus essential for viral proliferation [130]. Some conventionally used plant-derived medicines block these proteases [131–133]. Many plant secondary metabolites have already shown anti-SARS CoV action, in contrast to other antiviral capacities. These results raise the possibility of creating new drugs and chemicals that are more suited to the requirements of the patient.

1.7. Tinospora cordifolia

Tinospora cordifolia (Lour.) Merr. (Menispermaceae family) is a glabrous, deciduous climbing shrub from the. It has a considerable history of folkloric use and is accessible throughout the tropical regions of China and India [134,135]. The well-known Ayurvedic medication is made using *T. Cordifolia* aqueous extract. GuduchiGhanVati (*T. cordifolia)*, a traditional Indian medication with a broad range of pharmacological effects, is typically recommended as an immunomodulatory and antioxidant drug. GuduchiGhanVati has also been shown to be beneficial against SARSCoV-2 in recent trials [136,137]. 91 individuals aged 18 to 75 had their clinical data gathered between May 12 and June 15, 2020. Ayurveda's GuduchiGhanVati, a *Tinospora cordifolia* extract, was tested as a primary treatment for verified COVID-19 patients who had no symptoms to mild symptoms. Participants in this trial (identifier on ClinicalTrials.gov: NCT04480398) were split into two groups. The group consisted of 40 people who received GuduchiGhanVati orally twice daily after a meal for 28 days. Each tablet was 500 mg. 51 participants in the control group received traditional and conventional therapy [138]. In the control group, symptoms decreased by 11.7 % after an average of 1.8 days, while no one in the Ayurveda group experienced any exacerbated symptoms. At days 7 and 14, the virologic clearance in the Ayurvedic group was 100 %, while in the control group it was 15.6 % and 82.3 %, respectively. Statistics showed that the differences were substantial. The Ayurvedic group's average hospital stay was 6.4 days, compared to the control group's 12.8 days (Fig. 6).

To determine the effectiveness of aqueous extract of *Tinospora cordifolia* as a main therapy to manage COVID-19 infection in 46 asymptomatic patients, an open-label single-arm feasibility trial was done. 40 patients were the only ones to finish the 14-day experiment. There was no control group; all patients received two pills (1000 mg) twice daily for 14 days. No one displayed COVID-19 symptoms after the therapy. On days 3 and 7, the viral clearance rates were 32.5 % and 95 %, respectively. Data on day 14 showed that all test results for respondents were negative [136,137].

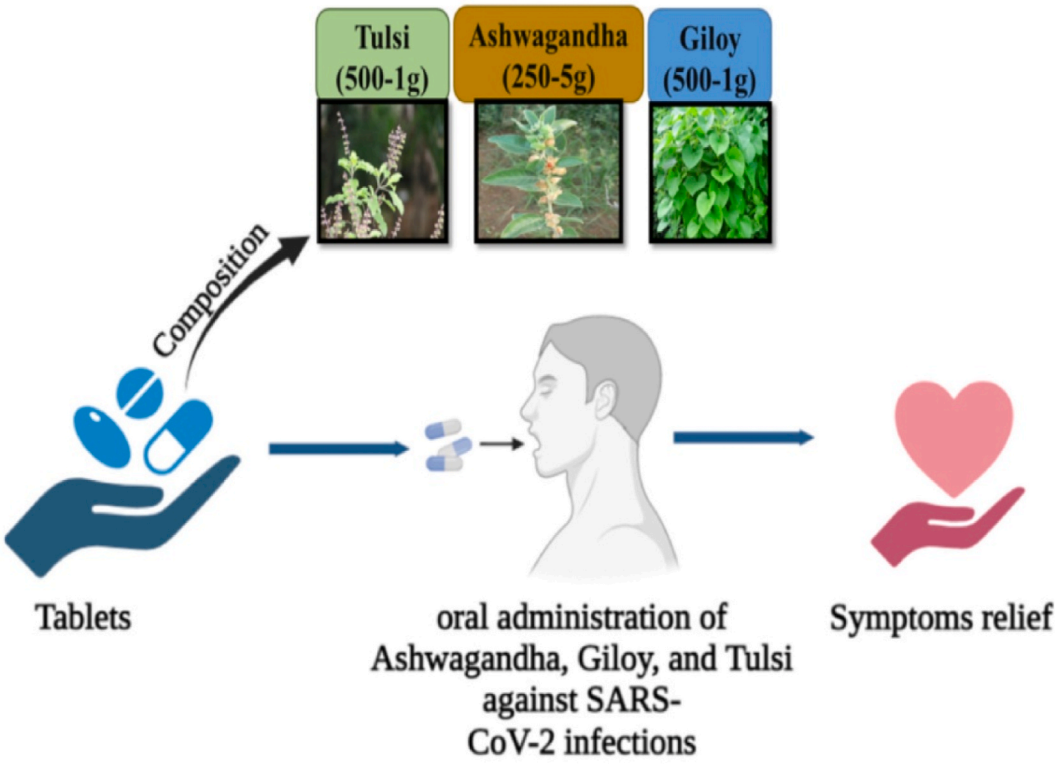

Fig. 7. Oral administration of Ashwagandha, giloy and tulsi tablets helped in relieving COVID-19 symptoms (Kulkarni et al., 2021).

1.8. Combination of Withania somnifera, Tinospora cordifolia and Ocimum sanctum

Withania somnifera (L.) Dunal of the Solanaceae family (commonly known as "ashwagandha"), *Tinospora cordifolia* (Lour.) Merr. of the Menispermaceae family (commonly known as "giloy"), and *Ocimum sanctum* L. of the Lamiaceae family (commonly known as "tulsi") are some herbal plants used in the Ayurvedic medical system. Researchers are evaluating the anti-COVID-19 activity of all these immunomodulatory plants because they all have shown promising immunity-boosting efficiency against infection. Recent research indicated that the bioactive metabolites of these will exhibit notable activity against SARS-CoV-2 infection. According to an in-silico investigation, the phytochemicals somniferin, isorientin 4′-*O*-glucoside 2″-*O*-*p*-hydroxybenzoate, withanoside V, tinocordiside, somniferine, and vicenin can stop the primary protease (M^{pro} or $3Cl^{pro}$) of a novel coronavirus strain [139]. To assess the efficacy of an Ayurvedic intervention as supportive treatment for patients with mild to moderate COVID-19, a community-based participatory study was carried out. 28 individuals with confirmed SARS-CoV-2 infections took part in an open-label study (ClinicalTrials.gov Identifier: NCT04716647) from October 9, 2020, to December 18, 2020. They received oral tablets of Ashwagandha, Giloy, and Tulsi as their main form of treatment. Patients received between 250 mg and 5 g of Ashwagandha, between 500 mg and 1 g of Giloy, and between 500 mg and 1 g of Tulsi, depending on their age, weight, and the severity of their symptoms. Then, for evaluation, information on the length of clinical recovery, the proportion of patients whose nasopharyngeal swab test resulted in a negative reading during the research period, and other clinical outcome data were acquired [140]. A seven-day recuperation period was suggested since Ayurveda provided better symptom relief. Data triangulation from several normal therapies revealed a statistically significant differential even though there was no control group. The Ayurvedic treatment can be beneficial, especially for those with mild to moderate COVID-19 symptoms (Fig. 7) [141].

1.9. Tinospora cordifolia and Piper longum

Tinospora cordifolia (Lour.) Merr. may also be used in conjunction with *Piper longum* L. (of the Piperaceae family), another well-known herb utilised in the Ayurvedic medical system. *P. longum* is also referred to as "Indian Long Pepper" and "Pippali" locally. While *P. longum* alone exhibits substantial antiviral activity, pippali is a traditional Ayurvedic supplementary ingredient that increases the bioavailability and absorption of the other active ingredients [142,143]. From October 8 to October 27, 2020, 28 individuals with confirmed COVID-19 were included in a placebo-controlled, randomised trial to assess the efficacy and safety of an Ayurvedic combination (Guduchi and Pipli) as a primary treatment. Guduchi (*Tinospora cordifolia*; 300 mg) and Pipli (*Piper longum*; 75 mg) were given to the participants twice daily [144]. On day 3 following therapy, 71.1 % of patients in the treatment group and 50 % of patients in the placebo group had made a full recovery. Only 60 % of the control group's patients had recovered by day 7, compared to 100 % of those

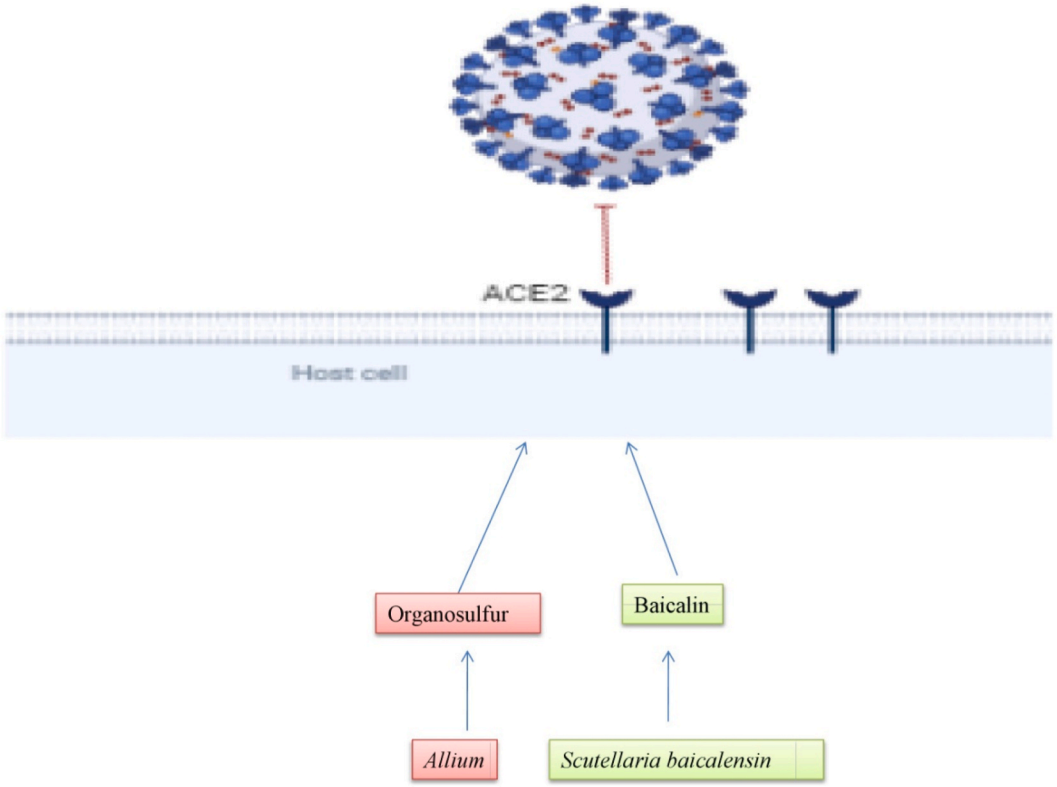

Fig. 8. Role of *Allium* and *Scutellaria baicalensin*in preventing COVID-19 infection by inhibiting contact of SAR-CoV-2 to the ACE2 receptor.

in the therapy group. In comparison to the control group, the therapy group had a greater recovery response rate. The probability of delayed healing process from infection in the treatment group was significantly decreased by 40 % [145].

1.10. Curcumin and piperine

In a double-blind, randomized, controlled study at a COVID Health Center (DCHC) in Maharashtra, India, Pawar and group (2021) sought to ascertain the effects of curcumin administered with piperine (to optimize absorption) on symptoms in patients with COVID-19. Patients in the study group got curcumin (525 mg) with piperine (2.5 mg) in tablet form twice daily, while patients in the control group received probiotics in addition to the standard COVID-19 treatment. For the length of the hospital stay, the effects of the curcumin/piperine treatment on primary and secondary outcomes were evaluated. As compared to patients in the control group, patients with mild, moderate, and severe symptoms who received curcumin/piperine treatment experienced early symptomatic recovery (fever, cough, sore throat, and breathlessness), less deterioration and a better ability to maintain oxygen saturation above 94 % on room air. Additionally, patients with moderate to severe symptoms looked to spend less time in the hospital under the influence of curcumin/piperine treatment, and fewer deaths were noted in this group. Oral curcumin combined with piperine given as an adjuvant symptomatic medication for COVID-19 could significantly lower morbidity and mortality while easing supply- and logistical-related strains on the healthcare system. To stop post-covid thromboembolic events, curcumin may be a secure and all-natural therapeutic choice [146].

1.11. Glycyrrhiza glabra

The main chemical in licorice (*Glycyrrhiza glabra*) root is glycyrrhizin. This substance is said to have antioxidant and anti-inflammatory properties that can encourage the body to produce interferons, and it has historically been used to treat conditions like gastritis, bronchitis, and jaundice [147]. The attachment of SARS-CoV agents to cells has been suggested to be reduced by glycyrrhizin, particularly during the first stage of the viral infection cycle [148]. Flavonoids, glycyrrhetinic acid, -sitosterol, and hydroxyl coumarins make up glycyrrhizin, which Cinatl et al. [96]found to have a strong anti-SARS-CoV action. Later, Pilcher (2003) [148] considered the licorice plant and glycyrrhizin as a potential technique of producing a pharmaceutical against SARS-CoV, adding that there is still a long way to go before producing a pharmaceutical against SARS-CoV. Other research further supported glycyrrhizin's anti-SARS-Cov action, and its beneficial antiviral properties have resulted in the publication of multiple review articles [149–154]. Glycyrrhizin has been identified as a possible inhibitor of SARS-CoV2 in an in silico investigation for the prediction of glycyrrhizin

behaviour for COVID-19 illness [31,155]. However, no research confirming the glycyrrhizin's in vivo efficacy has been discovered in the SARS-CoV. However, based on the encouraging findings of the aforementioned investigations, this substance may have the potential to be used in the creation of an anti-COVID-19 drug.

1.12. *Scutellaria baicalensis*

Scutellaria baicalensis derives its therapeutic properties from baicalin, one of the essential components of the Scutellaria family of plants. This flavone glucuronide has been utilised in the past to treat pulmonary atrial hypertension since it has been discovered to have anti-apoptotic and antioxidant characteristics. This substance's anti-SARS-CoV ability was initially demonstrated by Chen et al. (2004), who found that it had a stronger inhibitory impact than glycyrrhizin, interferon-alpha, and interferon-beta 1a, as well as a significantly lower toxicity concentration for cell lines in-vitro. This substance's antiviral properties were deemed to be so significant that a patent for the manufacture of anti-SARS medications using this biochemical molecule was later approved [156]. While the oral administration of the compound significantly increased the survival rate of mice infected with the influenza A virus, in-vitro testing of the extracted flavonoids from *Scutellaria baicalensis* also demonstrated significant anti-viral activity on the lipopolysaccharide activated cells [157]. However, no in-vivo research on baicalin's impact on model animals infected with SARS-CoV was found. The baicalin in-silico investigation for the COVID-19 illness simulation of the compound effect showed a favourable tendency of baicalin to inhibit Angiotensin-converting enzyme 2 (ACE2) (Fig. 8). A recent study further supports the theory that *Scutellaria baicalensis* can block the $3CL^{Pro}$ activity of the novel SARS-CoV-2 virus in vitro [158].

1.13. *Allium genus*

The Allium genus of plants *Allium porrum, Allium cepa* and *Allium sativum* are abundant sources of organosulfur compounds. Organosulfur compounds are typically the organic macromolecules with sulphur included into their biochemistry. According to a recent in-silico investigation for SARS-CoV-2, the organosulfur compounds from *A. porrum* can have a considerable potential in inhibiting the human ACE2 enzymes (Fig. 8), and as a result, they can potentially impede the connection of the SARS-Cov-2 to the cells [159]. The flavonoid quercetin is often found in the species of onion and garlic, and it can also be found as sulfonic substituents [160]. Chen et al. (2006) demonstrated quercetin-3-ability -galactoside's to inhibit $3CL^{Pro}$ of SARS-CoV. Additional research [161,162] supported the in-vitro suppression of $3CL^{Pro}$ of the SARS-CoV by quercetin and quercetin-3-galactoside. Additionally, it was discovered that quercetin 3D-glucoside may prevent the MERS-$3CL^{Pro}$Cov's from functioning [163]. This substance is one of the main natural ingredients that are targeted for the treatment of the COVID-19 disease because it has been shown to have little toxicity to cells in-vitro.

This section emphasised the significance of phytotherapeutic compounds as potential candidates in the development of medications to treat COVID-19. Safety worries still hang over the use of phytomedicine due to the novelty of the virus and the health issue it caused. The transformation of an intriguing chemical into a practical therapy option involves a variety of factors. The compound's remarkable pharmacokinetic profile, accessibility, bioavailability, and intellectual property are some of these traits. For the majority of the plants, there aren't enough data to ensure their quality, effectiveness, and safety. Pure substances should first undergo the necessary efficacy and safety testing, and their untested use is not advised. Marketing and well-established uses should only be permitted after there is scientific literature accessible that demonstrates the herbal product's active constituent's purity has a proven efficacy [164].

1.14. *Limitation*

The results of current study however be interpreted with limitations. Firstly, a small sample size that might not be typical of the entire population was used for the various case studies. Second, the case studies ignores co-morbidities when assessing pro-inflammatory markers, despite the fact that conditions like diabetes and hypertension make COVID-19 more severe. Therefore, keeping these factors in mind, randomized clinical studies of therapeutics are required to examine the functions of vitamin D and plant metabolites in the fight against COVID-19.

2. Conclusion

We have provided and reviewed the findings from numerous completed clinical trials in this article, which may result in useful new COVID-19 medications. To manage COVID-19, they could be standalone treatments or complementary or alternative medicines. The results of various studies suggest to the role of vitamin D status in the risk of COVID-19 infection based on low vitamin D levels. Numerous potential metabolites and plant-based herbal formulations delivered in a variety of ways produced positive results in preclinical research. These substances are currently undergoing various stages of clinical trials. So, to expedite laboratory-based research for the creation of molecular therapies to treat this and other pandemic circumstances, this review aggregated the majority of plants possessing antiviral properties onto a single platform. Natural plant products and medicinal plants are still thought to be viable alternatives for treating and preventing a wide range of illnesses.

However, there is a need for robust random controlled trial data on the function of vitamin D and plant metabolites in the treatment of COVID-19. Clinical trials that are now available provide a preliminary impression of the interaction. Even though the number of research is increasing, the majority of them are small observational studies with a significant bias risk, residual confounding, and reverse causality. The scientific community has also expressed concern that recent COVID-19 papers may not have undergone rigorous

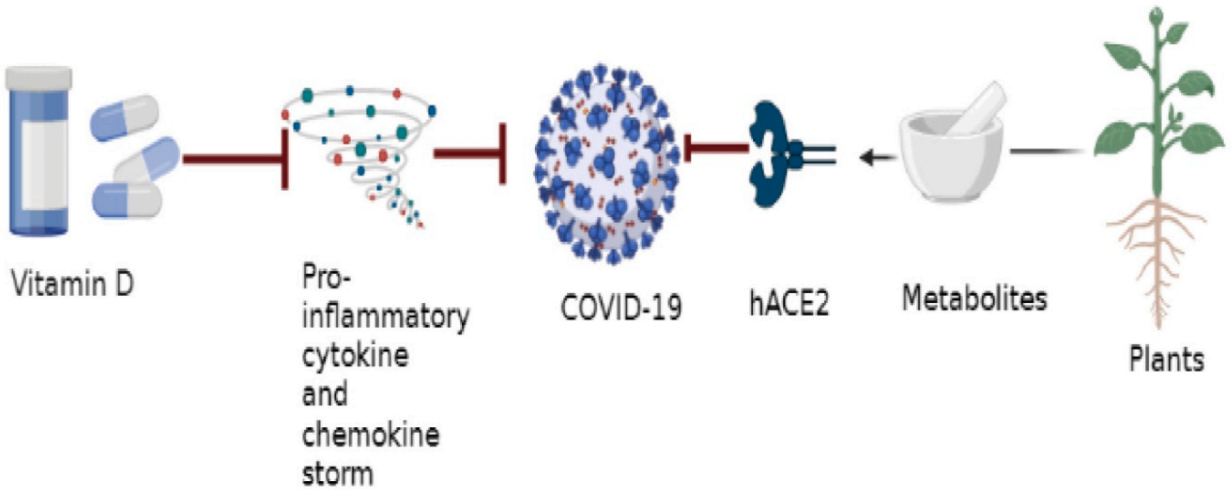

Fig. 9. Mode of action of Vitamin D and Plant metabolites in combating COVID-19.

peer review, which calls for caution when interpreting the data that have been made public. High-quality randomized controlled trials are necessary before making definitive claims about the positive effects of vitamin D and plant metabolites in this situation.

3. Future perspective

To prevent, diagnose, and treat the Covid-19 viral infection with vitamin D supplementation or/and acceptable plant metabolites or organic herbal medicinal plant products, certain interventional research is still needed. It is equally necessary to decipher if vitamin D and plant metabolite can together have a positive impact in enhancing immunity thereby preventing the infection. As stated the plant metabolites restrict the binding of SARS-CoV-2 glycoprotein to hACE2 and on the other hand vitamin D enhances immunity by reducing the cytokine and chemokine storm (Fig. 9). Therefore, research needs to take place to assess the possibility of these two working together to contain the infection.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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