



Efficacy of phytochemicals as immunomodulators in managing COVID-19: a comprehensive view

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Abstract Throughout history, disease outbreaks have worked havoc upon humanity, sometimes reorienting the history and at times, signaling the end of entire civilizations and the modern pandemic that the world is dealing with, is COVID-19 or SARS-CoV-2. A healthy immunity could be an ideal gear for resisting COVID-19 for neither medicines nor vaccines have been ascertained till date. In view of the present scenario, there is a demanding necessity to analyze innovative and valid techniques for forestalling and cure of COVID-19 by re-evaluating the structure of the natural compounds for drug designing. The Ayurveda has come forward by prescribing a lot of medicinal herbs for combating this dreaded disease. We have searched from sources in Pubmed and Google Scholar and found 1509 items. The search criteria were limited to the effect of phytochemicals in certain immunomodulatory aspects of viral infection. The original research papers related to the works on phytochemicals in the down regulation of NF- κ B, activation of NK and CD8+ cells, inhibition of inflammatory cytokine release and ROS scavenging were included in our study. Here, we try to focus on the immunoregulatory cells which have a vital aspect in COVID-19 and highlight the potential effects of the restorative use of phytochemicals as drugs or dietary supplements.

Keywords SARS-CoV-2 · Cytokines · Inflammation · Phytochemicals

Introduction

The world is currently dealing with the pandemic situation of COVID-19 caused by the novel corona virus i.e., SARS-CoV-2. It has been proclaimed in the whole world except Antarctica. SARS-CoV-2 affects lower respiratory tract which can be fatal. Transmittal of this virus can take place by personal proximity with affected person via respiratory droplets which are greater than 5–10 micro meter or droplet nuclei when less than 5 micro meter in diameter and unintended exposure with areas in the surrounding domain or with articles used by the diseased person. There is some evidence that SARS-CoV-2 may bring about intestinal contamination and also found in faeces. However, it has not yet been reported for faecal-oral transmission of the virus. The patients experience a wide spread severity of the disease. While very few patients need care of hospital, the pronounced effects in these people are lethal in certain cases. The elderly person are more presumably to suffer than middle aged and younger ones due to their immunocompromised state of health.

The novel corona virus is a single stranded positive sense RNA containing entity having the envelope (E), spike (S), nucleocapsid (N) and membrane protein (M), of which the spike and nucleocapsid proteins are obligatory in its life cycle [58]. The entry into the human cells is mainly facilitated by the binding of the Gln493 domain of the receptor binding motif of the spike protein to the host cell's ACE2 protein [67]. The replication process is quite complex upon entry into the host cell, which involves the action of the Replicase gene encoded enzyme by employing the

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negative strand of RNA for production of structural proteins of the viral progenies. The Nsp proteins aids in twisting the RNA while the N and M proteins bind to the genome and ER membrane respectively, preceding the transfer of the progenies to cell membrane for exocytosis [57].

Severe COVID-19 is induced not only by cellular impairment generated by the virus, but also by a reactive inflammatory storm that inflicts damage to the lungs and other organs. Acute respiratory distress syndrome (ARDS) follows after inflammation within lungs in severe COVID-19 on average after about eight to nine from the appearance of initial symptoms [60] which is the main cause of respiratory failure and fatality. The ARDS caused by the viral infection exhibits an imperfectly regulated renin-angiotensin-aldosterone system (RAAS). As a result of unbalanced RAAS activity serum levels of Angiotensin II become high which upregulates the AgII-ATRI axis. Due to this up regulation NF- κ B, disintegrin and metalloprotease17 are activated, causing the production of the two NF- κ B stimulators i.e., EGFR ligand and TNF α [11]. IL-6Amp is activated by Nf-KB and STAT3 after SARS-CoV-2 infection, causing further damage such as multiple inflammatory and autoimmune diseases [32]. Hirano et al. proposed that the enhanced proinflammatory cytokines are induced by IL6Amp. ARDS is caused by the liberation of inflammation-inducing cytokines IL-1, IL-6 and TNF. The lungs of these patients is filled with a jelly [37] which may be hyaluronan whose defective production and regulation is related to ARDS [12]. It has been reported as well that these cytokines can induce HA synthase 2 in CD31+ endothelium, EpCAM+ lung alveolar epithelial cells, and fibroblasts [6].

The traditional knowledge of the use of phytochemicals as remedial measures in various diseases has been passed on from generations. It has been accepted due to certain beneficial properties such as nontoxicity, easy availability, and ability to be included in diet, less side effects as well as cost affectivity. They can provide a supportive therapy in addition to the prescribed broad-spectrum antibiotics. There have been evidences globally of the antiviral potencies of the phytochemicals. We have kept in mind these facts and attempted to review the potency of certain phytochemicals as immunomodulatory agents to boost up the immune health of a person for fighting with this disease.

Method

This Review was conducted keeping in front a question, whether phytochemicals play a role in modulating the Immune system for combating COVID-19. The source of

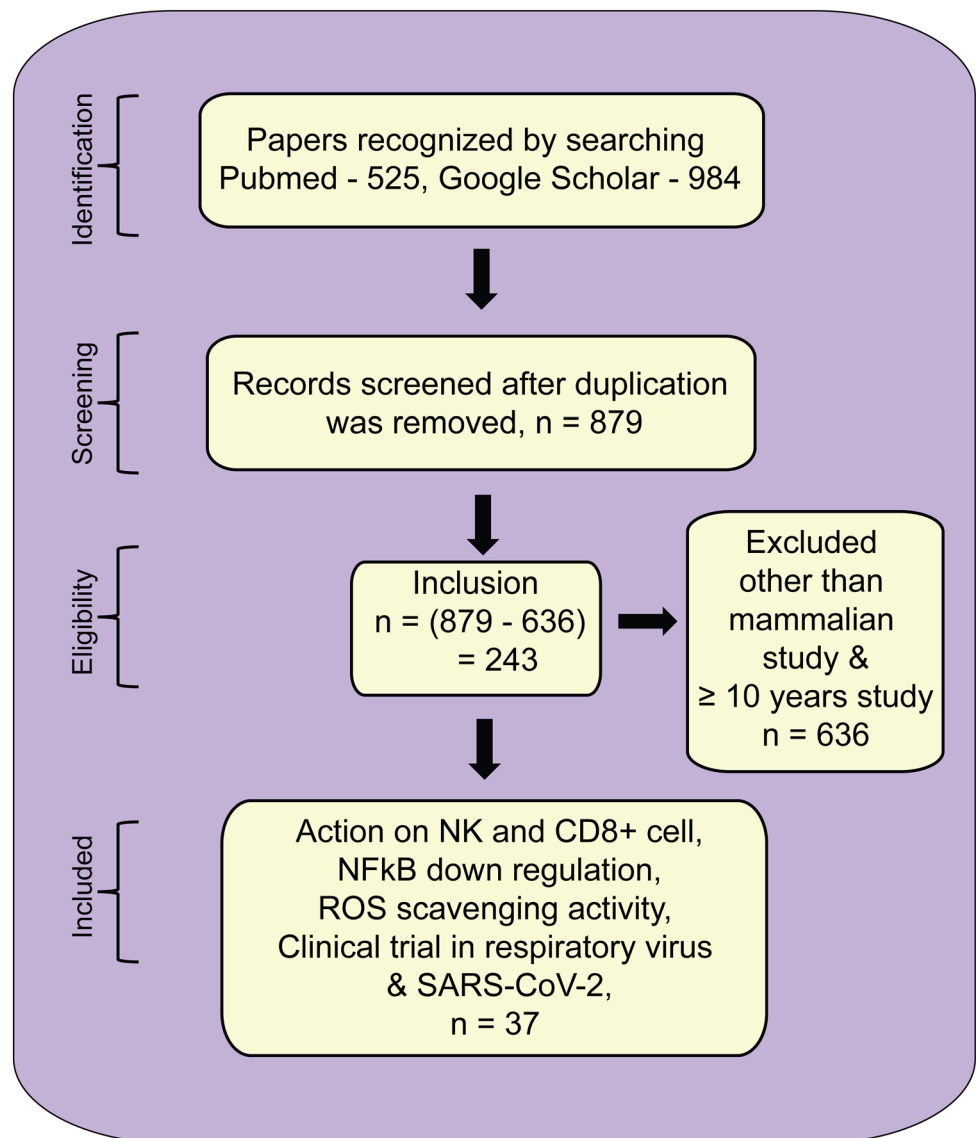
our study included Google Scholar and Pubmed and 1509 studies related to our search were found. We then short-listed those to 37 studies in accordance with Inclusion and Exclusion process (Fig. 1). The criteria taken into consideration were research studies involving the activities of phytochemicals respectively as immunomodulatory agents, studies involving active role of NK cells and CD8+ cells for production of anti-inflammatory cytokines and ROS scavenging activity and down regulation of NF- κ B. The clinical trial studies associated with antiviral effects against respiratory viruses and SARS-CoV-2 were included in our criteria as well. The studies more than or equal to 10 years old and other than Mammalian system were excluded.

COVID-19 infection and immune system

The virus alters the host's immunity in many aspects; lymphocytopenia, infective diagnostic markers like erythrocyte sedimentation rate, C-reactive protein, procalcitonin, and serum ferritin. Coexisting with this situation high levels of inflammation inducing cytokines and chemokines like tumor necrosis factor- α [TNF- α], interleukin [IL]-2R, IL-6, IL 7, IL 10, G-CSF, IP 10, MCP-1 and MIP 1A are observed. All these parameters were found to be elevated in extreme conditions in contrast with less severely infected people. In severely infected patients there is a significantly elevated level of CD14 + CD16+ cells in peripheral circulation as well as FCN1 + macrophage population in broncho-alveolar fluid leading to a surge in inflammatory cytokine and chemokine population [53]. The introductory defense mechanism against viral invasion includes IFN-I, which are recognized by the IFNAR receptors present at the plasma membrane in most cell types. The interaction of interferon with IFNAR prompts the phosphorylation of STAT1 causing their nuclear transposition and initiating activation of interferon-stimulated genes (ISG). Most ISGs are associated with inflammation and immunomodulation, hinder viral replication by stagnation of cell metabolism or cytokine secretion aiding in activation of the adaptive immunity. Delay in Interferon-I signaling nurtures the cumulating of pathogenic inflammatory monocyte macrophages (IMMs), yielding exalted inflammatory cytokine/chemokine levels, vascular permeability, and weakened virus-specific adaptive immunity in SARS-CoV patients [8]. The analogy of novel corona virus with SARS-CoV and MERS-CoV prompts us to speculate that it utilizes a similar strategy to destabilize innate immune response.

Different viral proteins may alter different points of the interferon signaling route, which are likely to aid in replication of virus, and increased level of pyroptosis thus leading to anomalous inflammatory reaction [53]. Reports of accumulation of monocytes and T cells in the lungs,

Fig. 1 Systematic chart to pinpoint all the selected publication



declined levels of hyperactive T lymphocytes in the peripheral circulation, lymphopenia in patients indicate that T cells accumulate at the site of infection away from the peripheral circulation to combat viral infection [53]. Cytotoxic T lymphocytes and NK cell population regulate the amelioration of the infection. The number of NK cells and T_C cells decrease while the expression of NKG2A increases in severe cases. Percentage of IFN- γ , IL-2 and TNF- α and granzyme B producing NK cells and T_C cells decreases with disease progression, suggesting the collapse of active T_C cells in infected people [68]. The IL 6 and IL 10-induced up regulation of NKG2A on the NK and naive CD8 + cells cause a sharp decline of the lymphocyte population to produce a versatile cytokine IFN- γ resulting in elevated neutrophil population in severe COVID-19 patients [3]. Serum levels of IL6 contribute significantly in disease severity due to its pleiotropic properties. The high

mortality rate of Covid-19 patients may be related to the elevated level of IL 6 Amp in aged patients [13] (Fig. S1).

Reactive oxygen species and disease progression

Several respiratory viruses either cause dysregulation of ROS formation or disrupt antioxidant mechanisms leading to increased recruitment of inflammatory cells at the infection site and subsequent oxidative cell damage respectively. The pathophysiological process of SARS-CoV-2 has a link with the overabundance of reactive oxygen species which is very crucial for raised inflammatory cell engagement at the point of infection [44]. According to some studies the commencement of acute lung damage in patients with SARS-CoV-2 infection relies on triggering of reactive oxidative stress mechanism which is integrated with non-specific immunity and turns on

transcription factors (NF- κ B), resulting in the rise of proinflammatory cytokines. It has also been suggested that 3CLpro-induced ROS-activated NF- κ B signal transduction pathway, might be considered a principal factor in SARS-CoV associated pathogenicity [44]. The pulmonary surfactant lipids and proteins are adversely affected by resulting inflammation and oxidative stress, thus disrupting gas exchange. The innate host defense mechanism mediated by surfactant–protein is also compromised. ROS is essential in controlling the immunological response correctly for viral infection clearance but an excessive amount of ROS oxidize cellular biomolecules like protein, membrane lipids responsible to destroy not only viral infected cell but also normal cells of the lung, heart resulting multiple organ failure [61]. Elevated Level of ROS implicated injury of lung tissue and epithelial barrier dysfunction with increased susceptibility to secondary infection [15] (Fig. S2).

Efficacy of phytochemicals in COVID-19

Indian herbal medicines are used by people globally and has been confirmed to reduce the ramifications of flu-like illnesses. Therapy involving phytochemicals may be a worthy, unconventional and safe alternative for treating viral diseases due to their negligible side effects and affordability. Ayurveda system of medicine has proposed a pragmatic plan for managing different stages of COVID-19 patients [41]. Phytochemicals inhibit viral adsorption, cell receptor binding, penetration into the host cell and regulating activation of intracellular signaling pathway [17]. They are reported to be potential in balancing antioxidants and free radicals in our body. We have tried to select certain phytochemicals among numerous, based on their efficacy on the pathways that have been focused in our discussion on the etiology of COVID-19.

A recent study found that Kamferol, curcumin, pterostilbene, bind with the C-terminal of S1 domain. It has also been reported that resveratrol, Fisetin, genistein quercetin, isorhamnetin, luteolin, and apigenin inter react with the S2 domain of spike protein. These compounds have significantly high binding affinity than hydroxychloroquinone. ADME (absorption, distribution, metabolism and excretion) exploration authenticated the attributes of these compounds for use as drugs [40]. A recent study has also revealed the efficacy of phytochemicals by displaying higher docking scores, stronger binding energies, and closer interactions with the conserved catalytic dyad residues (Cys-145 and His-41) of 3CLpro enzyme, than Nelfinavir, Prulifloxacin and Colistin [38]. Thus, it is evident that the phyto-formulations may be employed as potential therapy in COVID-19.

Fig. 2 Schematic representation of possible immunomodulatory pathway in COVID-19 targeted by phytochemicals. Virus sensing can trigger unregulated NF κ B induced inflammatory pathway to produce IL6, TNF α , MCP-1. CD8 + contribute upregulation of inflammatory cytokines and chemokines. Reduced NK cell population results less production of IFNs (IFN γ & IFN α). Cytokine induced inflammation promote accumulation of reactive oxygen species (ROS) and tissue damage in severe disease progression. Abbreviations- IL: Interlukin, IFN: Interferon, MCP-1: Monocyte Chemoattractant Protein -1, GM- CSF: Granulocyte macrophage colony stimulating factor, IP: Interferon gamma induced protein

Phytochemicals have anti-inflammatory and antioxidant properties. They decrease interleukin (IL)-12/IL-18-induced IFN- γ production, induces NK cell activity, block the release of proinflammatory cytokines or can act as inhibitors by masking the glycans present on the viral envelope. We have tried to focus on certain phytochemicals and their probable mode of action in modulating the person's immune response to combat the SARS-CoV-2 infection.

Result and discussion

We have analysed eighteen phytochemicals in respect to our selection criteria. These phytochemicals were curcumin, genistein, garlic extract, resveratrol, ashwagandha extract, tulsi (holy basil), ginseng, kumquat pericarp extract, prostratin, eugenol, capsaicin, eucalyptol, green tea extract, black tea extract, gingerol, cinnamon bark extract, sulforaphane and glycyrrhizin (Fig. 2). Out of these eighteen, eleven were chosen in accordance with their effectiveness on all the four criteria selected. Effectiveness of these phytochemicals on various viral proteins in addition to our specified immunomodulatory pathways have also been mentioned in a tabular form (Table 1). Of these, five phytochemicals (Curcumin, Garlic extract, Green tea extract, Sulforaphane and Ginseng) were chosen based on their application in clinical trial against SARS-CoV-2 or Influenza or respiratory virus (Table 2). The clinical trials of SinaCurcumin which is a registered nanocurcumin formulation of oral dose in Iran (IRC: 1228225765) involving three different parameters of COVID-19 gave significant positive results (Table 3). Curcumin, demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC) are three carotenoids in addition to volatile oils, proteins, carbohydrates, and resins, in turmeric ingredients. This needs further trial on a large group to be actually established into a valid drug against SARS-CoV-2. Clinical trial of ashwagandha in combination with Swasari Ras, Giloy Ghanvati, Tulsi Ghanvati and Anu Taila was done on mildly affected and asymptomatic patients (Clinical Trial Registry-India

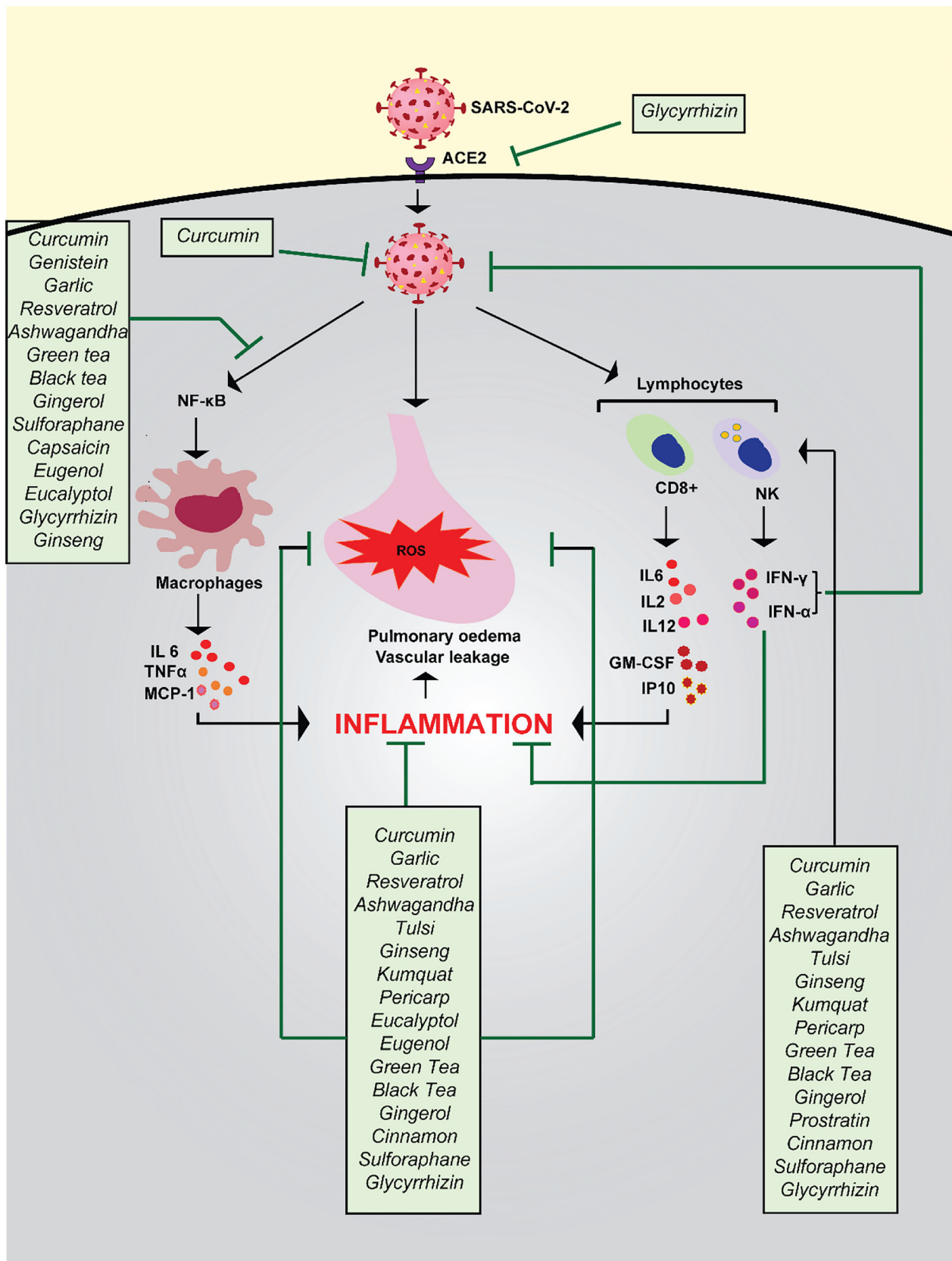


Table 1 Possible therapeutic targets of some phytochemicals in COVID-19

Name	Chemical nature/active component	Source	Actions based on our inclusion criteria	Other antiviral effects	References
Curcumin	Diferuloyl methane/polyphenols	<i>Curcuma longa</i> L	Yes	Binds to receptor binding domain (RBD) of S protein, nucleocapsid protein, membrane glycoprotein, RNA dependent RNA polymerase, direct or indirect inhibition of viral replication machinery by PI3K/Akt and NF-kB	[16, 59, 66]
Genistein	Isoflavonoid	Soyabeans, fava beans, coffee, <i>Flemingia vestita</i> , <i>F. macrophylla</i>	Yes	Interacts with spike protein's S2 domain	[46, 64]
Garlic extract	Allicin (S-allylcysteine sulphoxide/organosulphur compounds)	<i>Allium sativum</i>	Yes	Inhibit the ACE2 protein, targeting the PDB6LU7 protein, the M ^{pro} of SARS-CoV-2, Inhibit multiplication of virus	[4, 54]
Resveratrol	Polyphenol stilbene	Grapes, mulberries, peanuts	Yes	Hinder viral protein synthesis and expression of genes at different stages leading to prevention of viral replication	[26, 35, 43, 65]
Ashwagandha Extract	Alkaloids and steroidal lactones steroidal alkaloids, withaferin A and withanolide D	<i>Withania somnifera</i>	Yes	Increased the expression of Th1 cytokines, Bind to the substrate-binding pocket of SARS-CoV-2 Mpro	[20, 45, 55]
Green tea extract	Polyphenols (epigallocatech in 3-gallate)	<i>Camellia sinensis</i>	Yes	Agglutination and acidification effects on endosome & lysosomes, inhibits viral replication	[19, 28, 36]
Black tea extract	Polyphenols (theaflavin-3,3'-digallate)	<i>Camellia sinensis</i>	Yes	Theaflavins-1, Theaflavins-2 and Theaflavins-3 were found to suppress the SARS-CoV-2 replication by targeting RNA-dependent RNA polymerase (RdRp)	[25, 27]
Gingerol	Phenol	Ginger	Yes		[2, 10]
Sulforaphane	Isothiocyanate	Broccoli, green cabbage, red cabbage, turnip	Yes	Block the bronchoconstrictor hyperresponsiveness, arrest ARDS, activates Nrf2 and reinstate the age-related lapse of Th1 immunity	[7, 24, 50]
Glycyrrhizin	Triterpene saponin	<i>Glycyrrhiza glabra</i> roots	Yes	Binds ACE2, inhibits thrombin and alleviation of airway exudates, induces exogenous interferon, upregulation of p38, JNK and redox-sensitive signalling events	[29, 63]
Ginseng	Ginsenosides, saponin	<i>Panax ginseng</i>	Yes		[22, 52]

+ Denotes Activation,—Denotes Inhibition

PI3K (phosphoinositide 3-kinase), NFkB (Nuclear Factor kappa-light-chain-enhancer of activated B cell), ACE2 (Angiotensin Converting Enzyme 2), GABA (Gamma-Aminobutyric Acid), Intercellular Adhesion Molecule (ICAM)-1, Vascular Cell Adhesion Molecule (VCAM)-1, JNK (c-Jun N-terminal kinase). M Pro (main Protease)

(CTRI) (CTRI No. CTRI/2020/05/025273). It was found that the time of health restoration was brought down in response to the treatment and reduced serum levels of hs-CRP and pro-inflammatory markers, interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF- α) [9]. All these observations provide a constructive lead towards their

usage as drugs or dietary supplement in a dose specific manner for managing the progression of this viral disease.

Phytochemicals have a great potency to minimize the imbalance between free radicals and antioxidants where inflammatory cells are responsible for promoting pathogenesis. They are highly effective in arresting

Table 2 List of Some potential phytochemicals that have the possibility of use as therapeutic agents against SARS-CoV-2 in line with the evidences of their clinical trials (Source PUBMED)

Phytochemical	Clinical Trial	Formulation/ dosage	Result	References
Curcumin	SARS-CoV-2 Phase II	ArtemiC as dietary supplement	Not yet published	[42]
Garlic Extract	Conducted on common cold virus	120 healthy subjects were taken to record the efficacy of aged garlic extract supplementation (2.56 g/day) on proliferation of immune cells and flu symptoms of common cold Virus	The group consuming the aged garlic extract had reduced severity and less symptoms were noticed	[33]
Green tea extract (catechins)	Influenza infection	Gargling for 90 days	No conclusive evidence	[14]
Sulforaphane	Influenza virus	BSH for 4 consecutive days	Increases virus-induced peripheral blood NK cell granzyme B production	[31]
Ginseng	Acute Respiratory Infection Randomized, double-blind, placebo controlled clinical trial	100 subjects were involved in this study and randomly assigned to the KRG and placebo group KRG dose 3.0 g/day for 4 weeks as compared to placebo group	Statistically significant (P = 0.034) results regarding the occurrence of ARI were found to be lower in KRG group	[23]

BSH: Broccoli Sprout Homogenate, URTIs: Upper Respiratory Tract Infections, ARI; Acute Respiratory Infection, KRG: Korean Red Ginseng

inflammatory disorders by lowering the synthesis of pro-inflammatory cytokines. The phytochemicals have shown the presence of significant anti-inflammatory characteristic based on their scoring functions and together with the possibility of being formulated as drugs based on their physico-chemical properties, makes way for their future investigation in the production of innovative compounds which could prohibit the binding and fusion of S1 and S2 proteins of SARS-CoV-2. On the basis of recent evidences on the action of phytochemicals against inhibition of SARS-CoV-2 3CLPro activity and hence viral replication, possible role of the phytochemicals as potential drugs in COVID-19 has been intensified. The physical and chemical properties of the phytochemicals like melting point, molecular weight, affinity to lipids and their chemical configuration affect the method of drug formulation so as to make it more permeable. Nanomedicines that are highly target specific, evade cellular defense reaction, balance oxidative stress and can release the drug in reaction to specific signals can be efficacious for this purpose.

The antiinflammatory, immunostimulatory, antiasthmatic, anticold, and antioxidative properties of phytochemicals make them very popular choice in the diet of the pregnant women like cowpea, garlic, turnip, tomatoes, guava, cauliflower, drumstick leaves [21]. There have been positive reports of antioxidative activity of garlic based on random double blind clinical trials taking 400 mg of garlic and 1 mg of allicin per day for nine weeks in pregnant women having no side effects [1]. Obesity has been an

important factor leading to many comorbidities as Type I diabetes, cardiovascular diseases, kidney ailments etc. Phytochemicals have been shown to be effective in dealing with these conditions, however there have been reports for toxic effects in case of long term use of glycyrrhizin, curcumin, green tea and garlic extract [62]. Glycyrrhizin has been reported to cause physiological complications related to heart and blood vascular diseases when consumed daily at low doses [34, 47]. Further over consumption of green tea can cause kidney ailments [5], prolonged consumption of garlic at 250–1000 mg/kg dose can create adverse effects in lung and liver tissues [39], while continuous intake of curcumin at 0.9 to 3.6 g/day can give rise to diarrhea and nausea respectively [49]. However, there are reports of Curcumin at doses of 500 mg twice a day for 30 days orally was found to be nontoxic for humans [48]. It is very important to formulate correct doses for the consumption of these functional food plants to evade any sort of adverse reactions. Therefore, more long-term clinical trials become mandatory for finding a safe dose. Drugs in the form of nanoformulations such as green nanoparticles or carrier nanodrug or designing site specific nano medicines can be the way out so that high affectivity can be procured in spite of a low dose of the phyto formulation. Nanoparticle mediated drug delivery is a protected means of medicine application in pregnant women because of its low chance of interfering with the development of foetus [18].

Table 3 Clinical trials of Curcumin against SARS-Cov-2 in Iran approved by the Research Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1398.1314)

Phytochemical	Formulation	Dosage	Clinical Trial	Result	References
Curcumin	SinaCurcumin (Exir Nano, Tehran, Iran) Soft gelatin capsules containing curcuminoids as nanomicelles	Two 40 mg soft gel Capsules twice daily for 14 days	Non randomized, open labelled trial 20 COVID-19 patients in age group of 18 to 75 years with mild to moderate disease symptoms were taken in treated and placebo group respectively	Significant recovery rate (47.6%) was observed in treated compared to the control group (15%). Also, no degeneration (40%) of patients was observed in the treated group	[30]
		One 80 mg capsule twice daily for 21 days	Randomized, double-blind-placebo controlled trial study 40 severe COVID-19 patients and 40 mild cases of COVID-19 were chosen. The severe patients were divided into treated and placebo group each consisting of 20 individuals. 40 healthy individuals were involved in the trial	T regulatory cells were elevated significantly in moderately infected and serious patients and also alleviate the mortality rate in severe patients. FoxP3, TGF- β , IL-10, and IL-35 factors expression were notably upregulated in Nanocurcumin-treated both moderate and serious patients after treatment compared to before treatment; while, no substantial changes were found in the placebo-treated group	[51]
		160 mg (40 mgx4) Daily for 14 days + Betaferon 300 μ g subcutaneously every Other day until 5 days, Bromhexine 8 mg tablets every 8 h, and Atrovastatin 40 mg daily	Randomized, double blind placebo controlled study where 40 COVID-19 patients in the age group of 19–69 years were divided into treated and placebo group of 20 subjects each 40 healthy people were also included in the study	Statistically significant augmentation in almost all indicators displayed in Nano-curcumin group, including fever, cough and dyspnea were significantly subsided ($P < 0.0001$). IL1- β and IL-6 mRNA expression were decreased substantially in the treated group	[56]

Our observation regarding the potential act of phytochemicals as therapeutic agents in managing COVID-19 is further strengthened by the evidences from clinical trials of some phytochemicals like curcumin and ashwagandha against SARS-CoV-2 have further strengthened their beneficial use in boosting immunity against this virus. The phytochemicals like Garlic extract, Green tea extract, Sulforaphane and Ginseng applied in the clinical trial against virus causing respiratory diseases also indicate towards a possibility for their application in managing SARS-CoV-2. The clinical trial of Black Tea extract and Glycyrrhizin is also recommended by us keeping in view their use in Indian perspective, pointing towards their prospective role in challenging this virus. Further in vitro and in vivo studies regarding their combinatorial and dose specific effects should be undertaken so as to formulate adjuvant drugs to tackle

this dreaded viral disease. This will definitely go a long way in benefiting our country as far as its sizeable population is concerned and the continuance of the vaccination process with its respect.

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