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REVIEW

Efficacy and Safety of Add-On Plant-Based Drugs for COVID-19 Patients: A Review of the Randomized Control Trials

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Abstract: COVID-19 caused by the infection of SARS-CoV-2 is still a global concern. WHO reported that from 13 March to 9 April 2023, there were 3 million new cases and approximately 23,000 deaths, mostly occurring in the South-East Asia and Eastern Mediterranean regions, which is predicted due to the new Omicron variant, Arcturus XBB.1.16. Many studies have reported the potency of medicinal plants in enhancing the function of the immune system to combat virus infection. The literature review aimed to describe the efficacy and safety of add-on plant-based drugs for COVID-19 patients. The articles were explored on the PubMed and Cochrane Library databases, and published during 2020–2023. Twenty-two varieties of plants were used as add-on therapy for COVID-19 patients. These plants were *Andrographis paniculata, Viola odorata, Withania somnifera, Zingiber officinale, Curcuma longa, Ferula foetida, Centella asiatica, Thymus vulgaris, Citrus sinensis, Eugenia caryophyllus, Boswellia carterii, Elettaria cardamomum, Salvia rosmarinus, Piper nigrum, Alstonia scholaris, Picrorhiza kurroa, Swertia chirata, Caesalpinia crista, Cucurbita maxima, Tinospora cordifolia, Ocimum sanctum*, and *Allium sativum*. The best efficacy of an add-on therapy for COVID-19 patients was found in *A. paniculata* herbs as a single component in pharmaceutical dosage form or in combination with other plants. The safety of the plant has been confirmed. *A. paniculata* does not show interaction with remdesivir or favipiravir, however, caution and therapy drug monitoring is needed if *A. paniculata* is used in combination with lopinavir or ritonavir because a strong noncompetitive inhibition of CYP3A4 may occur.

Keywords: adjunctive therapy, flavonoids, plant-based therapy, immunomodulatory activity, clinical studies

Introduction

The outbreak of COVID-19 has been a global concern for more than three years. This pandemic has deeply affected the health sector. It is a highly contagious severe acute respiratory syndrome that eventually attacks and damages many organs. It was reported in the last 28 days (13 March to 9 April 2023) the incidence of 3 million new cases and approximately 23,000 deaths, mostly in the South-East Asia and Eastern Mediterranean regions. [1] The new Omicron variant, which is called Arcturus XBB.1.16, migrates from infecting mainly lungs and nervous tissue to the upper airways.[2]

COVID-19 patients show diverse clinical presentations ranging from asymptomatic, and mild to severe symptoms. Accumulating evidence suggests that comorbidities in SARS-CoV-2-infected individuals contribute to exacerbated outcomes, heightened symptom severity, and potentially elevated mortality risk.[3–5]

The virus, SARS-CoV-2, is an enveloped virus of spherical shape with a single-stranded RNA genome in the nucleus. It uses ACE2 to invade the human body (Figure 1) and the cellular protease TMPRSS2 for its spike (S) protein priming (proteolytic separation of the S1 and S2 subunits).[6]

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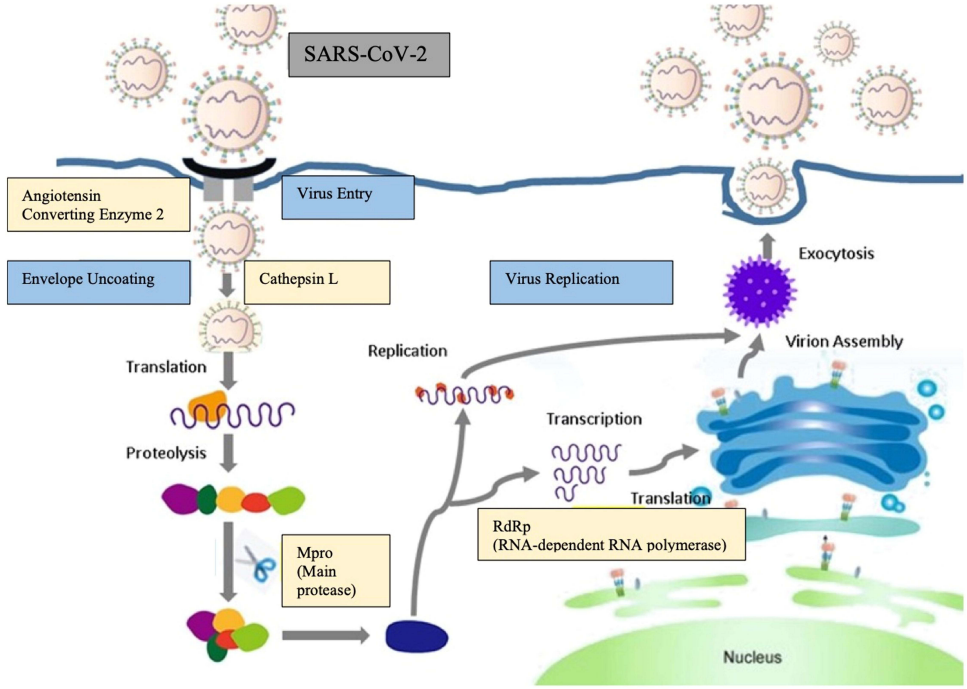

Figure 1 The cell cycle of SARS-CoV-2 in humans.

Infections are instigated by the attachment of transmembrane S glycoprotein to the peptidase domain of human ACE2.[7,8] The virus enters the target cells by binding the surface unit of the S protein (S1) to ACE 2. Viral fusion is primed by TMPRSS2 and the active S protein of SARS-CoV-2. The pH-dependent cysteine protease cathepsin L activates the S protein for fusion within the endosomal membrane. Mpro is a non-structural cysteine protease of SARS-CoV-2 that plays a role in the replication and transcription of the virus. RdRp (RNA-dependent RNA polymerase) is a non-structural protein of SARS-CoV-2 that works as a catalyst in the translation of viral RNA. SARS-CoV-2 uses an RdRp complex for the replication of their genome and for the transcription of their genes.[9,10]

At a time of worldwide anxiety, it is imperative to find long-term solutions to prevent the transmission of such pandemics, therefore, many studies have been focused on how to enhance the role of the immune system. The immune system can be classified into two functional categories: (1) the innate (non-specific) immune system and (2) the adaptive (specific or acquired) immune system. The immune system's architecture is organized into multiple layers, providing defenses at several levels. The skin serves as the primary and most evident barrier against infection. Physiological factors, such as body temperature and pH, also contribute to creating inhospitable environments for foreign organisms. Upon successful pathogen entry, the innate and/or adaptive immune systems become active. Both systems encompass a diverse array of cells and molecules that engage in intricate interactions to detect and eliminate pathogens. Detection and elimination rely on chemical bonding, where immune cell surfaces are adorned with various receptors. Some of these receptors bind to pathogens, while others interact with other immune cells or molecules, facilitating the complex signaling networks that underlie immune responses.[11,12] In a healthy organism, the immune system preserves internal homeostasis. The functionality and efficiency of the immune system are modulated by diverse exogenous and endogenous factors, leading to either immunosuppression or immunostimulant. Agents capable of normalizing or modulating pathophysiological processes are classified as immunomodulators.[12,13]

Many studies have reported the potency of medicinal plants in enhancing the function of the immune system to combat virus infection, however, no study reported on the safety of randomized control trials of plant extracts for patients with COVID-19. In this review, the efficacy and safety of add-on plant-based drugs for COVID-19 patients are discussed. Randomized controlled trials or clinical trials were chosen because they are prospective studies that evaluate the effectiveness of therapy. Before performing the trials, the researchers have to attentively choose the population, what

interventions to be compared, and the outcomes of interest. Through this review, readers will get insights into the results, outcomes, and benefits of using add-on plant-based therapy particularly plants with immunomodulatory activity for COVID-19 patients.

Materials and Methods

This review was based on the articles indexed in the PubMed and Cochrane Library databases, published during 2020–2023. The search was done using the keywords: (immune system AND flavonoids OR plants AND covid19 patients) AND (controlled trial" OR "randomized controlled trial" OR "randomized controlled trial" OR RCT[filter]). Inclusion criteria were limited to original articles written in English, plant-based drugs, accessible full texts, and randomized control trials or human studies. In vivo/in vitro/in silico studies, non-plant-based, or incomplete studies, were excluded. The titles and the abstracts of the articles included were further screened for their relevance to the topic of this study. Additional relevant studies were obtained from the citations in the selected articles. The detailed flowchart of the article searches and the results obtained are depicted in Figure 2.

Results

Of the 163 articles identified, 12 studies were reckoned to meet the eligibility criteria and these articles were included for analysis (depicted in Figure 2). Out of 12 studies, 11 studies are conducted in COVID-19 patients[14–24] and 1 study is conducted in post-COVID-19 patients.[25] There are 22 varieties of plants involved as add-on therapy for COVID-19 patients. These plants were *Andrographis paniculata* (Acanthaceae) in the dosage form of 150 mg extract in methylcellulose coated tablets (300 mg 3 times/day), *Viola odorata* (Violaceae) 1.5 g dried flower extract in 10 mL syrup (1.5 g 3 times/day), *Withania somnifera* (Solanaceae), *Zingiber officinale* (Zingiberaceae), *Curcuma longa* (Zingiberaceae), *Ferula foetida* (Apiaceae) 260 mg oleo-gum in tablets (260 mg twice/day), *Centella asiatica* (Apiaceae), *Thymus vulgaris* (Lamiaceae), *Citrus sinensis* (Rutaceae), *Eugenia caryophyllus* (Myrtaceae), *Boswellia carterii* (Burseraceae), *Elettaria cardamomum* (Zingiberaceae), *Salvia rosmarinus* (Lamiaceae), *Piper nigrum* (Piperaceae), *Alstonia scholaris* (Apocynaceae), *Picrorhiza kurroa* (Plantaginaceae), *Swertia chirata* (Gentianaceae), *Caesalpinia crista* (Fabaceae or Leguminosae), *Cucurbita maxima* (Cucurbitaceae) 5 mg squalene in microemulsion injection (5 mg twice/day), *Tinospora cordifolia* (Menispermaceae), *Ocimum sanctum* (Lamiaceae), and *Allium sativum* (Amaryllidaceae) 90 mg (three times/day). The number of trials, sample sizes, standard drugs used, clinical outcomes, and the adverse events for each included plant are tabulated in Table 1.

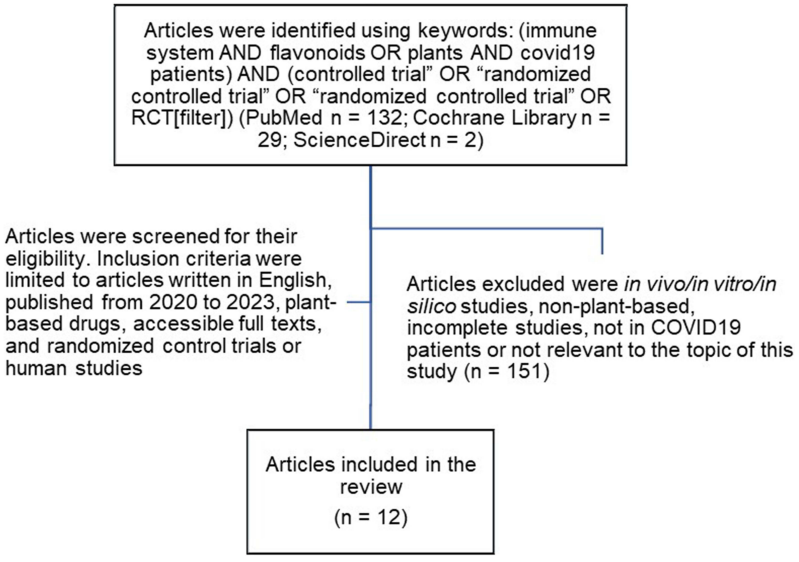

Figure 2 Flow chart diagram of the review process.

Table 1 Characteristics of the Study

Ref.	Sample Size (Patients)*	Gender Male (%)	Clinical Conditions	Name of Plant (Active Compound); Product Name; Dose	Standard Drug (SD)	Design of the Study	Length of Therapy (Days)	Efficacy or Clinical Outcomes	Safety Evaluation	Adverse Effect
Shanker et al[14]	62	69	Mild or moderate severity	***Andrographis paniculata*** standard extract (andrographolide, neo-andrographolide, 14-deoxy -11,12-didehydroandrographolide, and andrograpanin); CIM-MEG19 (contains 150 mg *A. paniculata* extract/ tablet)	SD = NSAIDs, antibiotics, antacids, and supplements	**Intervention Group** (n=38): SD + add-on therapy *A. paniculata extract* dosage 300 mg twice/day **Control Group**: SD + Redemsivir (n=24) and SD + Favipiravir (n=13)	14	Reduction of ESR, LDH, CRP, and D-dimer and an increase of IL-6 in the Intervention Group ($p \leq 0.05$)	Analysis of blood biochemical parameters (total protein, albumin, globulin, bilirubin, SGOT, SGPT, alkaline phosphatase, urea, and creatinine) before and after add-on intervention	No AE or SAE was observed in the Intervention Group. Five SAEs occurred in the Control Group
Adel Mehraban et al[15]	108	51.90	Mild or moderate severity	*Viola odorata L* (hydroquinone, gallic acid, resorcinol, pyrocatechol, catechin, and caffeic acid); Banafsheh syrup; 10 mL (contains *V. odorata* dried flower 1.5 g) three times/day	SD = acetaminophen or other NSAIDs for myalgia, bromhexine or dextromethorphan for cough, dimenhydrinate for nausea and vomiting, and replacement of water and electrolytes for diarrhea	**Intervention Group** (n=54): SD + add-on therapy *V. odorata* dried flower dosage 1.5 g in 10 mL syrup three times a day **Control Group** (n=54): standard antivirus if needed + placebo syrup	7	Faster recovery and a significant decrease in severity scores: cough (P = 0.025), myalgia (P = 0.036), headache (P = 0.037), and diarrhea (P = 0.044) in the Intervention Group	Analysis of blood biochemical parameters (WBC, neutrophil percentage, lymphocyte percentage, RBC, HGB, platelets count, CRP, ESR), oxygen saturation, pulse rate, and BP before and after add-on intervention. Vital signs (body temperature, heart rate, respiratory rate, and blood pressure) and laboratory tests (complete blood count and CRP) were assessed. Any AEs were recorded via phone call during the study and through history-taking and physical examination at the final visit.	No AE or SAE was observed in both groups. AE was monitored daily based on Common Terminology Criteria for Adverse Events (CTCAE) ver. 5
Chitre et al[17]	175	69.8	Moderate plus at least one respiratory symptom (nasal congestion, sore throat, cough, breathing difficulty); and at least one constitutional symptom (aches/pains, fatigue, headache, chills, or sweats). Patients were confirmed positive with Delta or B.1.617 variant.	Ashwagandha (*Withania somnifera), Boswellia carterii, Zingiber officinale*, and *Curcuma longa*; BV-4051; 2 tablets twice/day	SD = Redemsivir	**Intervention Group** (n=89): SD + add-on therapy (dosage 1776 mg of BV-4051 twice/ day after meals) **Control Group** (n=86): SD + placebo	14	Alleviation of fever in the Intervention Group on day-4th = 34% compared to the Control Group = 16.9%, a reduction in the duration of illness, and a decrease in IL-6, ERS, and LDH in the Intervention Group on day-14th. An increase of TNF-alpha was observed in both groups.	Safety was assessed by monitoring and recording all adverse events (AEs), regular physical examinations, hematology, chemistry, and 12-lead-electrocardiograms.	Moderate AEs (increase in LDH=1.5%, CRP=1.5%, and TNF=1.0%) were reported. These AEs were observed in 13 patients, 4 were in the Intervention Group and 9 were in the Control Group, but resolved during the study period, and were considered not related to the product

Hasanpour et al[18]	50	70	Mild or moderate severity	Ferula foetida (oleo-gum) (butyl propenyl disulfide and methylthiopropyl 1-propenyl disulfide) Covexir; 1 capsule (260 mg of F. foetida oleo-gum) twice a day	SD = Azithromycin 500 mg once daily, hydroxychloroquine 200 mg twice daily for 5 days, and acetaminophen 500 mg tablets were used as standard care of treatment	**Intervention Group** (n=30): SD + *F. foetida* oleo-gum add-on therapy (dosage 260 mg twice a day) **Control Group** (n=20): Antivirus + placebo	7	An improvement in the clinical presentations (cough, shortness of breath, myalgia, anorexia, anosmia, and sense of taste) of patients in the Intervention Group was observed. A 27.01% reduction in CRP level in the Intervention Group, with no significant difference compared to the Control Group ($p > 0.05$)	An infectious disease specialist and a nurse visited and scored the patients' clinical manifestations in the baseline (day-0) and the follow-up sessions (day-3 and day-7) were performed by a nurse.	No specific AEs were observed in the Intervention Group. Gastrointestinal complications such as bloating and nausea were merely recorded in a few patients
Damle et al[19]	95	48	Mild or moderate severity and the presence of co-morbidity like diabetes and hypertension	*Andrographis paniculata, Centella asiatica, Withania somnifera*; ATRICOV 452 (dosage 1 g) three times/day	SD for mild severity patients = Favipiravir 1800 mg day-1 continued with Favipiravir 500 mg day-2 to day-7; SD for moderate severity patients = Oseltamivir 75 mg 1-0-1 for 5 days	**Intervention Group** (n=48): SD + ATRICOV 452 (dosage 1 g) three times/day **Control Group** (n=47): SD + placebo three times/day	14	In the Intervention (ATRICOV 452) Group and the Control Group (placebo), symptoms resolved in 100% of patients by day-15. An improvement in the levels of CRP, leucocyte count, NLR, D-dimer, PCT, LDH, and IL-6	The levels of CRP, leucocyte count, NLR, D-dimer, PCT, LDH, and IL-6 were measured as indicators of recovery	No AE. All organ system was normal in function.
Hawkins et al[25]	40	0	Post-COVID-19	*Thymus vulgaris, Citrus sinensis, Eugenia caryophyllus, Boswellia carterii* (essential oils); Longevity; 4 drops for 10 minutes inhalation, twice/day	N/A	**Intervention Group** (n=20): 4 drops of essential oils, inhaled, twice/day **Control Group** (n=20): 4 drops of a placebo, inhaled, twice/day	14	Significantly lower fatigue (p=0.002)	N/A	One participant in the Intervention Group reported experiencing headaches and withdrew on day 13; no other AE was observed
Shakeeb et al[20]	64	N/A	Mild or moderate severity; detected positive no more than 24 h	*Elettaria cardamomum, Salvia Rosmarinus, Piper nigrum* (1,8-cineole); Recovereez Forte; 500 mg, three times/day	SD = Oral Prednisolone in tapered dosage for 10 days, 100 mg × 3 times for the first 3 days, 100 mg × 2 times for the next 3 days, and 100 mg × 1 time for the last 4 days	**Intervention Group** (n=32): SD + Recovereez Forte 500 mg, three times/day **Control Group** (n=0.32): SD	10	Negative from COVID-19 at the fifth day (37.5%), with recovery from symptoms such as fever, cough, sore throat, and breathlessness compared to the control group by day 5.	Monitoring changes in the vital markers (liver function, renal function, serum electrolyte)	There were no patients in the Recovereez Forte group who dropped out owing to major side effects. Patients taking Recovereez Forte had minor gastrointestinal side effects such as gastroesophageal reflux. There were no negative changes in vital markers (liver function, renal function, serum electrolyte) during the study

(*Continued*)

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Table 1 (Continued).

Ref.	Sample Size (Patients)*	Gender Male (%)	Clinical Conditions	Name of Plant (Active Compound); Product Name; Dose	Standard Drug (SD)	Design of the Study	Length of Therapy (Days)	Efficacy or Clinical Outcomes	Safety Evaluation	Adverse Effect
Singh et al[21]	74	64.9	Mild or moderate severity	*Alstonia scholaris R.* Br., *Picrorhiza kurroa Royle* ex. Benth, *Swertia chirata* Pexbex. Karst, *Caesalpinia crista*; AYUSH-64; two tablets (500 mg each) three times/day	SD = Acetaminophen 500 mg SOS, Cetirizine 10 mg OD, Vitamin C 500 mg BD, and Azithromycin 500 mg OD (for 5 days)	**Intervention Group** (n=40): SD + Ayush-64 **Control Group** (n=40): SD	30	Reduced the levels IL-6 and d-dimer (p = 0.007), higher decrease in CRP level, LDH, serum ferritin and HRCT chest score compare to control group	Monitoring changes in the vital markers (liver function, renal function, serum electrolyte)	No AE. None of the participants required invasive or non-invasive oxygen therapy or developed complications
Ebrahimi et al[22]	30	67	Mild or moderate severity; respiratory symptoms (including dyspnea, chest pain, or discomfort); oral temperature > 38°C and SpO2 < 93%	Pumpkin seed oil (Squalene); injection of 5 mg SQ microemulsion twice/day	SD = 150 mg chloroquine (equivalent to 250 mg chloroquine phosphate), two tablets on the first day and one tablet every 12 h for a total of 10 days, or 400 mg hydroxychloroquine on the first day and then one tablet every 12 h for 10 days and Lopinavir/ Ritonavir (200/50) every 12 h for 10–14 days and heparin 5000IU subcutaneous TDS (for body mass index [BMI] ≥ 40, 7500 IU SC TDS) or Enoxaparin 40 mg SC once a day (for BMI ≥ 40, 40 mg SC BID) and Oxygen therapy	**Intervention Group** (n=15): SD + Pumpkin seed oil (Squalene); injection of 5 mg SQ microemulsion twice/ day for 6 days **Control Group** (n=15):	7	There was a significant difference between 2 groups in the need for oxygen therapy s after 7 days of treatment (p = 0.020); no fever at least for 2 days (p = 0.025); Cough alleviation (p = 0.010); improvement in chest CT scan (p = 0.033)	All participants were monitored for adverse events including anaphylaxis, ALT or AST elevation more than 2.5-fold beyond the normal upper limit, total bilirubin elevation more than 1.5-fold beyond the normal upper limit, acute pancreatitis, and diarrhea.	No clinical or laboratory adverse effects were observed within 7 days of admission
Devpura et al[23]	95	81	No or mild severity	*Tinospora cordifolia, Withania somnifera, Ocimum sanctum*; tablet 500 mg, twice/day	Placebo (tablets with identical looks and feels, composed of wheat flour as a major ingredient along with excipients and binders)	**Intervention Group** (n=45): Oral administrations of 1 g of Tinospora cordifolia and 2 g of traditional herbal-mineral formulation and 0.5 g each of Withania somnifera and Ocimum sanctum) twice per day for 7 days **Control Group** (n=50): Placebo	7	Reduced the time to recovery; decreased serum levels of hs-CRP and pro-inflammatory markers, IL-6 and TNF-α	Safety profile outcome was studied.	N/A

Shohan et al[24]	60	56.7	Severe; Non-ICU admission; uninterrupted O2 therapy supported by reservoir bags; arterial blood O2 saturation under 93%	Quercetin; 1000 mg once/day	Remdesivir: First day 200 mg (IV injection); Second to fifth day: 100 mg (IV injections daily); Favipiravir: First day: 3200 mg (1600 mg PO BD); Second to fifth day: 1200 mg (600 mg PO BD); Vitamin. D: 1000 IU daily; MgSO4: 250 mg orally twice a day (based on serum Mg level); Famotidine: 40 mg oral daily; Zinc sulfate: 30 mg daily; Vitamin C: 500–1000 mg daily; Dexamethasone: 8 mg daily IV injection	**Intervention Group** (n=30): SD + Quercetin 1000 mg, once/day **Control Group** (n=30): SD	7	Reduced the hospitalization period; more effective decreased serum levels of q-CRP (p=0.004), LDH (p=0.032), and ALP (p=0.002) in the intervention group	Not mentioned in the study	AE related to SD
Taghavi et al[16]	141	49	Comply with the latest version of The Scientific Committee of the National Staff for COVID-19 Disease Management	*Allium sativum* (thiosulfate (allicin), S-allyl cysteine sulfoxide (alliin), ajoenes, vinyldithiin, and diallyl sulfide); Gallecina; 1 capsule 90 mg three times/day	Remdesivir at a 200-mg loading dose as an intravenous infusion on day 1 of hospitalization, followed by a maximum maintenance dose of 100 mg/day from day 2 to 5; subcutaneous enoxaparin 40 mg daily, oral bromhexine syrup 5 mL thrice daily, oral multivitamin syrup 5 mL daily, oral zinc sulfate syrup 10 mg daily, and oral acetaminophen tablets 500 mg every 6 hours as needed	**Intervention Group** (n=101): **Control Group** (n=95): SD + placebo	5	The clinical status distribution on day-6 and at discharge was not statistically significant between the 2 groups. On the day of discharge, the degree of body temperature significantly differed between the Intervention Group (36.92°C) and the Control Group (36.98°C) (P = 0.04). The CRP level on the day of discharge was below the normal range (<7 mg/L) in both groups, making it clinically non-significant.	Safety profile outcome was studied.	GI side effects were documented in 20% of patients in the Intervention Group when compared with 12% of patients in both groups starting from day-1 and day-2. The most frequent complications were abdominal pain, nausea, vomiting, and diarrhea. Although the distribution of GI complications did not differ significantly between the 2 groups (P = 0.12), GI complications in the Intervention Group were approximately double when compared with those in the Control Group.

Note: *Participants who completed the study.

Abbreviations: SD, standard drugs; NSAIDs, non-steroid anti-inflamation drugs; AE, adverse events; SAE, severe adverse events.

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The articles analyzed were published from 2020 to 2023. The total number of participants involved was 1042 COVID-19 patients, with the majority of the patients being male gender (56.83%). The duration of the studies ranged from 5 to 30 days. However, one study included in this review was performed on 40 post-COVID-19 female patients.

The studies used standard-of-care drugs, eg, a combination of NSAIDs (acetaminophen 500 mg)[14–16,18,21] or SAIDs (prednisolone),[20] antibiotics (azithromycin 500 mg),[18,21] chloroquine or hydroxychloroquine,[18,22] H1R antagonists (cetirizine 10 mg for allergy or dimenhydrinate for nausea),[15,21] anticoagulants (enoxaparin 40 mg),[16,22] antitussive (bromhexine or dextromethorphan),[15,16] antacids or H2R antagonists (famotidine),[24] and supplements (Vitamin C 500 mg). The antiviral drugs used were remdesivir (in general) or favipiravir (for mild severity symptoms) or oseltamivir (for moderate severity symptoms) or a combination of lopinavir/ritonavir. Most of the studies reported a reduction of symptoms or faster recovery and a decrease in inflammatory responses (IL-6, C-reactive protein, and D-dimer) in the Intervention Group (plant-based add-on therapy) compared to the Control Group. Moreover, 6 studies indicated the safety of the add-on plant-based therapy as proven by no AEs observed in the Intervention Group patients.

Efficacy

All twelve reviewed studies reported the efficacy of the plant-based add-on therapy (Table 1). Efficacy was evaluated by measuring the levels of inflammatory responses, either IL-6 or C-reactive protein or D-dimer or all (10 articles), and/or the hospitalization period (5 articles), and/or the severity of the symptoms, eg, cough, myalgia, fever, sore throat, fatigue (7 articles). Not all studies showed their data, some of them only reported general qualitative statements, eg, an improvement in inflammatory responses or a significant decrease in inflammatory markers.

The efficacy data of the plant-based add-on therapy for COVID-19 patients in this review were obtained by comparing the changes (calculated in %) in IL-6, CRP, and D-dimer levels (Table 2) before and after the intervention.

It is interesting to find out that the aerial part of *Andrographis paniculata* plants (CIM-MEG19 tablet) has shown the best efficacy as an add-on therapy for COVID-19 patients.[14,19] This drug showed a statistically significant ($p < 0.05$) reduction in CRP (53.58%) and D-dimer (22.04%) levels as well as the ESR (erythrocyte sedimentation rate). However, an increase in IL-6 (21.88%) was observed, although in general, the patients in the Intervention Group showed no AEs or SAEs.[14] *A. paniculata* was also studied in a combination with other plants (ATRICOV 452 capsule) and resulted in a decrease of IL-6, CRP, and D-dimer levels.[19]

Moreover, the bulb of garlic (*Allium sativum*) was studied as an add-on therapy in reducing CRP in mild-severity hospitalized patients with COVID-19. Although the result was not clinically significant compared to that of the placebo group, the add-on therapy using *A. sativum* could reduce 62.55% CRP level compared to the baseline. However, this plant has caused GI discomfort in 20% of the patients.[16]

A study in post-COVID-19 patients was included in this review because the term post-COVID-19 syndrome has recently procured global recognition among scientific communities. The pathogenesis of post-COVID syndrome involves multiple mechanisms that result in various clinical manifestations.[26] The post-COVID-19 patients were given 10 minutes of inhalation of essential oils containing a mixture of *Thymus vulgaris, Citrus sinensis, Eugenia caryophyllus*, and *Boswellia carterii* (essential oils) twice per day for 14 days, which resulted in a significant decrease in fatigue in the Intervention Group. Nevertheless, one participant in the Intervention Group reported experiencing headaches and withdrew on day-13. No other AE was observed.[25]

Safety

The safety of the add-on therapy was evaluated in 10 of the 12 studies, by analyzing the hematologic parameters (WBC, neutrophil percentage, lymphocyte percentage, RBC, hemoglobin, platelets count) and/or blood biochemical parameters (total protein, albumin, globulin, bilirubin, SGOT, SGPT, alkaline phosphatase, urea, and creatinine), and/or inflammatory biomarkers (ESR, LDH, CRP, and D-dimer), and/or physical examination (oxygen saturation, pulse rate, and BP), and/or by monitoring the AEs, before and after add-on intervention. The most frequently reported side effects are mild GI discomfort (bloating and nausea) and headache. None of the studies reported severe side effects. All studies confirmed the safety of the add-on therapy.

Table 2 Efficacy of the Plant-Based Add-On Therapy on the Inflammatory Responses in Patients with COVID-19

Name of the Plant (Trade Name of the Drug)	Analysis of the Chemical Constituents	Reference	Before Add-On Intervention			After Add-On Intervention		
			IL-6 in pg/mL	CRP in mg/L	D-Dimer in ng/mL	IL-6 in pg/mL	CRP in mg/L	D-Dimer in ng/mL
A. paniculata (CIM-MEG19 tablet)	1. Andrographolide 2. Neo-andrographolide 3. 14-deoxy-11,12-di-dehydro andrographolide 4. Andrograpanin	Shanker et al (2023)[14]	7.13 ± 2.33	21.5 ± 41.5	188 ± 51.8	+21.88%	−53.58%	−22.04%
V. odorata (Banafsheh syrup)	1. Hydroquinone 2. Gallic acid 3. Resorcinol 4. Pyrocatechol 5. Catechin 6. Caffeic acid	Adel Mehraban et al (2023)[15]	N/A	19.09 + 12.89	N/A	N/A	−2.57%	N/A
W. somnifera, B. carterii, Z. officinale, C. longa (BV-4051 tablet)	N/A	Chitre et al (2022)[17]	N/A	N/A	N/A	N/A	+1.5%	N/A
F. foetida (Covexir capsule)	1. Butyl propenyl disulfide 2. Methylthiopropyl 1-propenyl disulfide	Hasanpour et al (2022)[18]	N/A	N/A	N/A	N/A	−27.01%	N/A
A. paniculata, C. asiatica, W. somnifera (ATRICOV 452 capsule)	N/A	Damle et al (2022)[19]	N/A	N/A	N/A	Decrease	Decrease	Decrease
E. cardamom, S. rosmarinus, P. nigrum (Recovereez Forte)	N/A	Shakeeb et al (2022)[20]	N/A	N/A	N/A	Increase	Increase	N/A
A. scholaris, P. kurroa, S. chirata, C. crista (AYUSH-64)	N/A	Singh et al (2022)[21]	5.8	5.0	0.35 + 0.21	−18.97%	−26.00%	−40.00%
T. cordifolia, W. somnifera, O. sanctum (Ayurvedic Medicine)	N/A	Devpura et al (2021)[23]	N/A	N/A	N/A	Decrease	Decrease	Decrease
N/A	Quercetin	Shohan et al (2022)[24]	27 + 8	66.9 + 23.9	872 + 452	−33.33%	−68.01%	−41.17%
A. sativum	N/A	Taghavi et al (2023)[16]	N/A	13.7	N/A	N/A	−62.55%	N/A

Notes: "-" value decreases after the intervention; "+" value increases after the intervention.

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Discussion

SARS-CoV-2 infection rapidly stimulates $CD4^+$T lymphocyte cells to become pathogenic T helper (Th)1 cells and produces granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-6. Eventually, it invigorates inflammatory factors engendering a cascade of interactions and cytokine storm.[3] C-reactive protein (CRP) and IL-6 were appointed as markers to determine the severity of COVID-19. An elevation of IL-6 indicated the worsening of the disease, while a decrease indicated the effectiveness of therapy.[27]

IL-6, a cytokine featuring pleiotropic activity, works by stimulating the production of acute-phase proteins, eg, CRP, and blocking the production of albumin. IL-6 also contributes a part to the acquired immune response by activating immunoglobulin production and T-cells generation. IL-6 stimulates the differentiation or proliferation of various non-immune cells; thus, discontinued production of IL-6 governs the instigation of various diseases.[28]

CRP is a pentameric protein produced in the mitochondria of hepatocytes. The level of this protein increases in correlation with inflammation. CRP is released when oxidative stress due to the presence of reactive oxygen species which opens the mitochondrial permeability transition pore. CRP is primarily induced by the IL-6 action on the gene controlling the CRP transcription process.[29] The normal level of CRP is < 10 mg/L; however, it elevates rapidly within 6–8 hours and reaches its maximum in 48 hours from the onset of inflammation.[30] The level of blood CRP has been reported to range from 20 to 50 mg/L in patients with COVID-19.[31,32]

Immunomodulator Activity of the Plants

Several studies reported that most of the medicinal plants used in the treatment of COVID-19 have similar mechanisms, including the regulation of apoptosis and immune response.[33–35] For example, a clinical study proposed that standardized *A. paniculata* extract had increased both T and T helper cells, and significantly increased IFN-γ, IL-4, and decreased IL-2 at day-30 in participants with absolute lymphocyte counts of 1000–3000 cells/mm^3. There were no treatment-related adverse effects following standardized *A. paniculata* extract intake for 30 days.[35] In a multicenter randomized open-label trial involving adult patients hospitalized with mild to moderate COVID-19, an injection containing 9-dehydro-17-hydro-andrographolide and sodium 9-dehydro-17-hydro-andrographolide-19-yl sulfate (popularly known as Xiyanping injection) was proven a safe and effective in accelerating symptom resolution (eg, fever and cough) and rapid SARS-CoV-2 clearance.[36]

Andrographolide, the main active compound *A. paniculate*, are reported to exhibit various pharmacological activities including immunostimulator, antiviral, antibacterial, and anti-inflammation.[37,38] Andrographolide was proven could inhibit the function of hepatitis C virus NS3-4A serine protease, a protein essential for RNA replication and signal transduction.[39,40] In addition, an in silico study concluded that andrographolide, a major diterpenoid lactone of *Andrographis paniculata*, was confirmed to effectively prevent the fusion of SARS-CoV-2 to hACE2 by breaking the salt bridge in hotspot-353 and occupying the site where the virus binds (Lys353 and Asp38).[7] Moreover, andrographolide could inhibit the inflammatory cytokines in LPS-induced RAW264.7 cells by blocking the NF-kappaB/MAPK signaling pathway,[41] thus this diterpenoid lactone may reduce the occurrence of cytokine storms in COVID-19 patients.

A previous study investigated the immunomodulatory effect of *W. somnifera* (Ashwagandha) extract, revealed that after the 30-day period, participants in the intervention group showed a significant increase ($p < 0.05$) in immunoglobulins (IgA, IgM, IgG, IgG2, IgG3, and IgG4), cytokines (IFN-γ, IL4), and T-helper 1 (Th1) cytokines, CD4+ and CD8+ T cell counts, and natural killer NK cells, whereas, in the placebo group, these cells showed a significant decrease ($p < 0.05$) and no alteration in the levels of immunoglobulins and cytokines ($p > 0.05$).[42]

Herbal-Drug Interactions

Herbal-drug interactions are frequently observed, particularly in patients with chronic conditions, such as diabetes, hypertension, and psychiatric or neurological disorders, and therapy using medications with narrow therapeutic index, including anticonvulsants, anticoagulants, antiplatelet agents, antiarrhythmics, immunosuppressants, neuroleptics, anti-diabetic drugs, and specific antibiotics like vancomycin.[43,44]

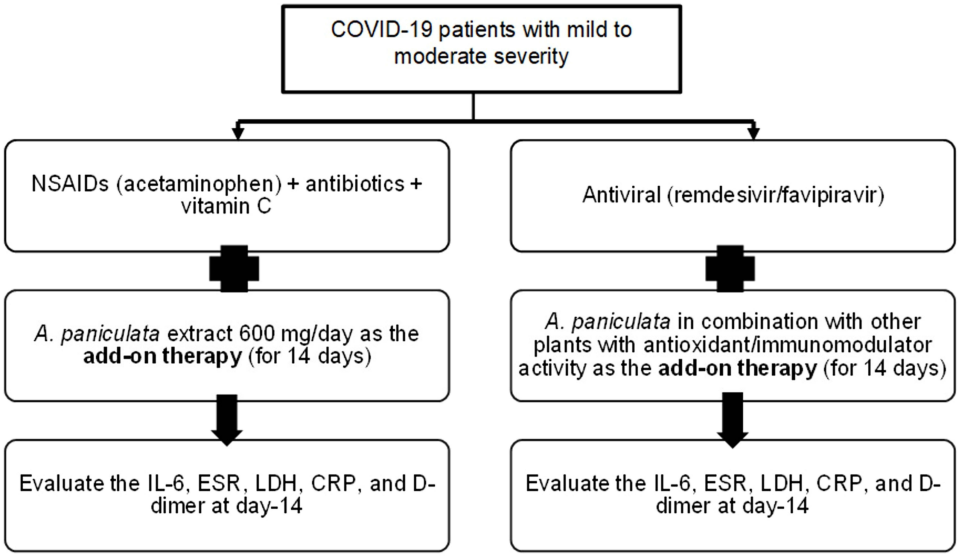

Figure 3 Proposed add-on phytotherapy algorithm for COVID-19 patients.

Standard-of-Care in the management of COVID-19 comprises various antiviral agents, such as remdesivir, favipiravir, and oseltamivir, alongside the extensive employment of antibacterial medications, antitussives, expectorants, and supportive care, which increase the potential of herbal-drug interactions. Although the clinical study review in this article assessed the safety profile of herbal therapies, none addressed the potential interactions between the herbal compounds and other drugs employed in the studies.

It is widely acknowledged that pharmacokinetic and pharmacodynamic interactions represent the two fundamental categories of drug interactions observed in clinical settings. Most of these interactions are associated with the role of principal drug-metabolizing enzymes or/and drug transporters, including cytochrome P450 (CYP450) enzymes and/or P-glycoprotein (P-gp). An in vitro CYP450 study in human liver microsomes indicated that remdesivir possesses a moderate inhibition towards CYP3A4, CYP2C8, and CYP2D6, while *W. somnifera* had no inhibitory effect alone or in combination with remdesivir. Thus, *W. somnifera* was considered safe to be co-administered with the substrates of CYP3A4, CYP2C8, and CYP2D6. However, caution is warranted in prescribing AYUSH-64, a polyherbal formulation, along with CYP2C8 substrate drugs.[45]

Although we cannot find other studies reporting the herbal-drug interaction related to those employed in the clinical study, several studies had reported justifiable findings. A recent study disclosed that an injection prepared from andrographolides, the major active components of *A. paniculata* (Burm. f.) had affected the pharmacokinetics of lopinavir/ritonavir through strong noncompetitive inhibition of CYP3A4 in a time-dependent manner.[46] Hence, extreme caution needs to be taken when *A. paniculata*, as a parenteral dosage form, is co-administrated with lopinavir/ritonavir for COVID-19 treatment.

Taken together, we propose an add-on phytotherapy algorithm for COVID-19 patients using *A. paniculata* as a single add-on therapy or in combination with other plants possessing antioxidant or immunomodulatory activity (depicted in Figure 3).

Conclusion

The efficacy of plant-based add-on therapy for patients with COVID-19, in general, was evaluated by measuring the levels of inflammatory responses, and/or the hospitalization period, and/or the severity of the symptoms, eg, cough, myalgia, fever, sore throat, fatigue. The most effective and safest plant-based drugs for COVID-19 patients are *A. paniculata* as a single component in pharmaceutical dosage form or in combination with *W. somnifera* and *C. asiatica* or with *T. cordifolia* and *O. sanctum*. The safety of the plant-based add-on therapy has been confirmed and proven by no occurrence of AEs or mild GI discomfort. Caution and therapy drug monitoring is needed if *A. paniculata*

is to be administered in combination with lopinavir/ritonavir because a strong noncompetitive inhibition of CYP3A4 may occur thus altering the pharmacokinetics of the antivirals.

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Disclosure

The authors declare no potential conflicts of interest in this work.

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