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Review Article

Highlights on the recent clinical studies and inventions in the use of natural products in the management of Covid-19

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Abstract

Natural products (NPs), long regarded for their medical qualities, have recently seen a rise in interest as the world seeks viable therapies and prevention measures for COVID-19. Many reports have been published on the role of NPs in managing COVID-19. This article highlights the recent noteworthy clinical developments and inventions concerning the application of NPs to manage the COVID-19 pandemic. The non-patent literature for this review was obtained from PubMed, whereas patent information was obtained from the Espacenet databases. Recent clinical trials have explored the role of many NPs (spirulina; curcumin + piperine; xanthohumol; CurcuRouge®; virgin coconut oil; thyme oil; licorice extract; pomegranate juice; Ayurvedic and Chinese herbal formulations) in managing COVID-19. Multiple NPs formulations and compositions (dieckol; isobracin; phloroglucinol compounds; propolis + xylitol; Virofree TM; NRICM102; Terminalia chebula tannic acid + punicalagin; Cypress tree extract + Chlorine dioxide; Saussurea costus) with antiviral and immune-boosting potential have been recently patented for use in COVID-19 management. Many inventions are foreseeable, including new delivery systems of existing anti-COVID-19 NPs, derivatives of anti-COVID-19 NPs, drug repurposing of the marketed NPs, and new combinations (two or more NPs; NPs + existing anti-COVID-19 drugs; NPs + vaccine; NPs + monoclonal antibodies). Nonetheless, there is a great deal of room for innovation in the use of NPs in the control of COVID-19. Accordingly, NPs have the potential to play an increasingly important role in global healthcare to manage COVID-19 as studies continue.

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Introduction

The SARS-CoV-2 virus, which gave rise to the COVID-19 pandemic in late 2019, fundamentally changed daily life, the economy, and worldwide health. It started in December 2019 when new coronavirus infections were discovered in Wuhan, China. On January 30, 2020, and March 11, 2020, respectively, the World Health Organization (WHO) proclaimed it a public health emergency of international concern and a pandemic. In a few months, the virus had spread to almost every nation on earth (1). Since the introduction of COVID-19, there have been about 777 million confirmed infections and about 7.1 million deaths worldwide (Table 1) (2-5).

Table 1: General information about COVID-19 (3-5)

Risk factors / High-risk population	Elderly; immunocompromised people; pre-existing conditions (diabetes, hypertension, etc.)
Transmission (Incubation period)	Direct contact with the infected person/ asymptomatic carrier and airborne transmission (2-14 days)

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Signs and Symptoms	Fever; cough; shortness of breath; loss of taste/ smell; fatigue; sore throat; muscle/body ache; pneumonia; multiorgan failure; death in severe cases
Diagnosis	RT-PCR (Gold standard); antigen/antibody tests; chest imaging (for severe cases)
Treatment	Drugs (remdesivir; molnupiravir; nirmatrelvir; dexamethasone; monoclonal antibodies); Vaccines (Pfizer-BioN Tech (mRNA); Moderna (mRNA); AstraZeneca (Viral vector); Johnson & Johnson); Natural compounds (curcumin, resveratrol, quercetin, thymoquinone, etc.)
Challenges	The emergence of new variants (Delta and Omicron); viral mutations leading to immune escape

NPs provide different chemical frameworks for drug development, including lead molecules for antiviral medicines or adjuncts to existing treatments. NPs have helped identify COVID-19 therapies because they contain bioactive chemicals with therapeutic potential. Drug development has relied on these plant, marine, and microorganism-derived compounds. NPs' role in COVID-19 drug discovery shows their continuous relevance in modern medicine, providing alternative and complementary treatments while meeting the pressing demand for novel therapeutic agents (6-12). Traditional Chinese Medicine (TCM) herbal medications were also tested for COVID-19 relief and immunological enhancement (13-14). Literature is available on the use of NPs for the management of COVID-19 (6-14). Many of these articles have also provided clinical trial information about the use of NPs to manage COVID-19. However, new clinical trial reports are regularly published, mandating writing an update on these clinical trials. Recently, many natural product-related inventions have also been published. This study updates and summarizes the recent developments in COVID-19 management with NPs, focusing on clinical studies and patents published between January 2023 and December 2024. In this work, we examine and analyze recent clinical trial data (2023–2024) utilizing NPs, highlighting newly published patents and patent applications for COVID-19 prevention, treatment, or symptom management. This study will be valuable for researchers and healthcare professionals working on the development of COVID-19 treatments.

The non-patent literature for this review was searched on PubMed (https://pubmed.ncbi.nlm.nih.gov/advanced/#) on January 6, 2025, utilizing the keywords (COVID-19 or SARS-CoV-2) in the title of PubMed articles. The results were further filtered using article type (clinical trial) and publication date (January 2023 to December 31, 2024). This search provided 1271 references. The articles related to clinical trials concerning NPs, herbal products, polyherbal formulations, plant extracts, phytochemicals, and traditional medicines were segregated. The patent data was searched on Espacenet databases (https://worldwide.espacenet.com/patent/search).

Recent Clinical Studies

The recent non-patent literature of clinical studies involving NPs for managing COVID-19 collected from PubMed is discussed below.

The TOGETHER trial (NCT04727424; Phase 3) sponsored by Cardresearch in Brazil examined if spirulina helps high-risk outpatient COVID-19 patients in Brazil. The study was conducted on 1126 participants, wherein 569 were dosed with spirulina (1 g two times a day for 14 days) and 557 were assigned to the placebo. Spirulina treatment did not produce any clinical benefit over placebo and both groups shared a common side effect profile (15).

Curcumin is a known healthcare remedy. A highly absorbable (100 times than normal curcumin) composition of curcumin curcuRouge® (cR) has been developed and assessed for its efficacy against COVID-19 in clinical trials (CRB5200002; Japan). The study examined the efficacy of the cR oral capsule (360 mg two times a day; 71 patients) and placebo (67 patients) for seven days among COVID-19-diagnosed patients. The COVID-19 patients on cR therapy demonstrated a significant decrease in body temperature and required lesser antipyretics than placebo suggesting better anti-inflammatory effects of cR. However, the effect of cR therapy on the progression of COVID-19 was not statistically significant, mandating additional large-scale clinical studies (16).

Piperine and curcumin are well-established natural remedies, wherein piperine may increase curcumin absorption. A clinical study assessed the effect of the curcumin-piperine co-supplementation in 40 COVID-19 patients. The COVID-19 patients received three capsules of curcumin (500 mg)-piperine (5 mg) each day for 7 days versus placebo. The curcumin-piperine group exhibited a decrease in serum aspartate aminotransferase and C-reactive protein, but an increase in hemoglobin than placebo. The findings suggest curcumin as a complementary option for managing COVID-19 patients (17).

A Chinese herbal medicine (CHM) formulation comprising ten herbs, namely Platycodonis Radix (Jiegeng), Atractylodis Macrocephalae Rhizoma (Baizhu), Poria (Fuling), Glycyrrhizae Radix et Rhizoma (Gancao), Schizonepetae Herba (Jingjie), Mori Cortex (Sangbaipi), Isatidis Radix (Banlangen), Forsythiae Fructus (Lianqiao), Lonicerae Japonicae Flos (Jinyinhua), and Pseudostellariae Radix (Taizishen) was evaluated for COVID-19 prevention (9 g; twice a day for 7 days; 1720 patients) versus control group (443 patients). The CHM formulation group did not produce any side effects and was effective in preventing COVID-19 (18).

The effect of virgin coconut oil (VCO; 0.6-1.2 ml per kg body weight) on relieving symptoms and inflammation among 40 unvaccinated COVID-19 patients has been reported (PHRR220718-004884; Philippine) in comparison to the control group of 40 COVID-19 patients. The VCO resolved the symptoms and normalized the C-reactive protein in two weeks among mild to moderate cases of COVID-19. The study also suggested the use of VCO as an adjunct therapy for COVID-19 regardless of meal timings (before, after, or coupled with a meal) (19).

Oner and Cengiz studied the effects of thyme oil inhalation aromatherapy (3 times a day for 5 days) on 70 COVID-19 patients' symptoms, vital signs, and hemodynamic parameters concerning the control group of 70 COVID-19 patients. The thyme oil treatment was effective in decreasing the body temperature, respiratory rate, pulse rate, and other COVID-19 symptoms (cough, muscle/joint pain, diarrhea, dizziness, and headache). These findings suggested the effectiveness of thyme oil in decreasing vital signs, and hemodynamic parameters among COVID-19 patients (20).

A study compared the effects of the extracts of Tinospora cordifolia (oral; 500 mg; 43 patients), Adhatoda vasica (oral; 500 mg; 50 patients), and a combination of both (oral; 250 mg of each extract; 43 patients) for COVID-19 symptom therapy, severe

development prevention, and viral clearance (CTRI/2020/09/028043; India). All three groups of patients recovered from COVID-19 without demonstrating any adverse effects. The combination group produced faster viral clearance than the other two groups. The study suggests that Adhatoda vasica acts as a HIF-1α modifier, while Tinospora cordifolia exerts immunomodulatory effects (21).

A Brazilian group evaluated the effect of EPP-AF (Standardized Brazilian green propolis extract; oral dose of 900 mg per day; 98 patients) among hospitalized COVID-19 patients versus placebo (90 patients) for 10 days (BeeCovid2; NCT04800224). There was less risk of secondary infections in the EPP-AF group, and it was thought to be safe to use. There was also no statistically significant correlation between the use of EPP-AF and a shorter hospital stay. Green propolis was suggested to be an inhibitor of transmembrane serine protease 2 and ACE2 anchoring (22).

Licorice extract contains glycyrrhizin, which is reported to possess antioxidant, anti-inflammatory, and antiviral activity. Licorice (760 mg three times a day for seven days) was tested for efficacy and safety in 60 COVID-19 patients versus the control group. Licorice normalized C-reactive protein and alanine transaminase without any adverse effect in its group but did not lessen COVID-19 symptoms mandating further clinical studies among a larger population (23).

A clinical study (IRCT20150711023153N2) assessed the effect of pomegranate juice (500 mL per day for two weeks) on the complete blood count (CBC) and inflammatory status among 40 hospitalized COVID-19 patients versus placebo. This research concluded that pomegranate juice may help fight SARS-CoV-2 infected patients by slightly improving inflammatory state, CBC outcomes, and interacting with S-glycoprotein and ACE2 (24).

The efficacy of the AYUSH 64 tablet (a conventional polyherbal ayurvedic drug; 500 mg tablet; two tablets twice a day for 12 weeks) has been evaluated along with standard care in 140 COVID-19 patients (CTRI/2020/06/025557). Each tablet of AYUSH comprised aqueous extracts of the bark of Alstonia scholaris (100 mg), the rhizome of Picrorhiza kurroa (100 mg), the whole plant of Swertia chirata (100 mg), and seed powder of Caesalpinia crista (200 mg). AYUSH 64 and standard care enhanced COVID-19 recovery, hospitalization, and health. It was safe and well-tolerated, recommending the next stage of a clinical phase III trial (25).

Over thousands of years, Sudarshana cúrna, a polyherbal Ayurvedic medication comprising 49 medicinal herbs, has been used to treat various infectious fevers. Recently, Link Natural Sudarshana (LNS) tablets have been assessed in 83 COVID-19 patients (Phase II trial; SLCTR/2021/002; U1111-1263-2664) versus placebo (88 patients) for 10 days. LNS safely lowered viral load, improved symptoms, normalized C-reactive protein, and restored lymphopenia faster than placebo through ACE 2 suppression (26).

The efficacy of the combination of Withania somnifera (Ashwagandha; two tablets of 250 mg each twice a day; 25 patients) and Zingiber officinale (Shunti; two capsules of 500 mg each twice a day; 25 patients) against COVID-19 has been performed for 15 days versus standard care (23 patients) (CTRI/2020/08/027224). Ashwagandha and Shunthi expedited viral clearance and clinical recovery among COVID-19 patients, achieving this safely and with good tolerability (27).

Xanthohumol is an established antioxidant and anti-inflammatory molecule. Xanthohumol reduces inflammation by inhibiting FXR activity and NF-κB-dependent gene production, including IL-1β, IL-6, IL-8, IL-12p70, TNFα, and interferon γ. Therefore, Xanthohumol (4.5 mg/kg body weight for 7 days) was assessed for its efficacy in 50 COVID-19 patients versus the control group. Xn therapy significantly reduced plasma IL-6, D-dimer, and NLR levels compared to the control group, indicating Xn's potential for use as a promising adjuvant therapy for COVID-19 (28).

Echinacea fights viruses. One study (IRCT20130522013423N2; 20 COVID-19 patients) examined the effects of Echinacea extract syrup on lower respiratory tract outcomes in COVID-19 patients. In COVID-19 patients, Echinacea extract syrup (Imogen syrup; 5 cubic centimeters three times a day for 5 days) did not improve acute lower respiratory tract infection symptoms, warranting further clinical studies for Echinacea extract on COVID-19 patients with pulmonary complications (29).

Ginger possesses antiviral, anti-inflammatory, and antioxidant properties. There was insufficient clinical evidence linking ginger to COVID-19. Ginger (1000 mg 3 times a day for 7 days; 49 COVID-19 patients) was tested for clinical and paraclinical efficacy and safety (IRCT20200506047323N1). It was found that ginger had little effect on patients' clinical and paraclinical characteristics (30).

Recent patent literature

The latest inventions concerning NPs for managing COVID-19 obtained from the Espacenet patent database are summarized in Table 2.

Table 2: Recent inventions concerning NPs for managing COVID-19

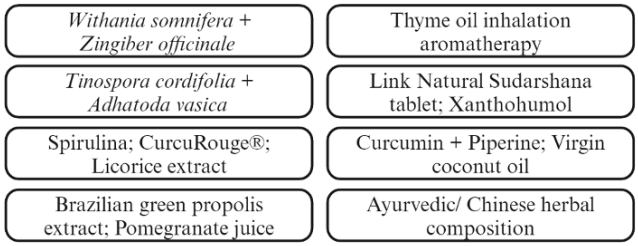
S. No.	Patent/Application Number (Applicant)	Summary
1	**US2024115622A1** (Servidence)	This publication relates to a formulation (toothpaste, rinse, nasal spray) capable of reducing the viral load in the nasopharynx and saliva comprising propolis (0.25-2.0 weight %) and xylitol (0.25-3.0 weight %) as active agents for the prevention and treatment of covid-19. The formulation may also include additional agents like a carrying agent, a moisturizing agent, a thickening agent, an abrasive agent, a flavoring agent, a surfactant agent, and a foaming agent. The results also showed the formulation can protect cells from coronaviral infection (31).
2	**WO2024135941A1** (Jeonnam Bioindustry Foundation)	This publication discloses the use of Dieckol (derived from Ecklonia cava) for preventing or treating COVID-19. This document also provides a pharmaceutical composition comprising an extract of Ecklonia cava for inhibiting the proliferation of alpha, beta, gamma, delta, and omicron variants of SARS-CoV-2 (32).

3	**CN115837020A** (Shanghai Jiaotong University)	This publication declares isobracin (a flavonoid isolated from St. John's Wort) compositions for inhibiting COVID-19 infection. This document mentions that isobrazirin inhibits the expression of COVID-19 protease 3CLpro by covalently binding to thiol or cysteine (33).
4	**CN117045752A** (Ningbo Sunguobao Iot Tech Research Institute)	This publication asserts a stable, reliable extract composition with a good safety profile comprising tangerine, unicorn fruit, reed, and Eucheuma for prevention and/or treatment of COVID-19 through the inhibition of angiotensin-converting enzyme 2. The extract is claimed to be effective against SARS-CoV-2 and its mutant viruses (34).
5	**CN117957009A** (Duan Meinan)	This publication states a method for treating/preventing long-term COVID with an herbal composition (Virofree TM) comprising a mixture of grape seed extract (10-50% w/w), acerola cherry extract (5-30% w/w), olive leaf extract (5-30% w/w), marigold extract (1-20% w/w), green tea extract (1-20% w/w), pomegranate extract (1-20% w/w), yeast beta-glucan (1-20% w/w), and soy extract (1-20% w/w). Virofree can target various stages of viral entry and replication, especially against the δ and o variants, and the consequences, including iron-dependent cell death, cytokine storm, ARDS, and pulmonary fibrosis (35).
6	**CN118045073A** (Yunnan University Of Traditional Chinese Medicine)	This publication reveals the use of phloroglucinol compounds in the preparation of coronavirus 3CLpro target protein inhibitors. The phloroglucinol compound may be extracted from Dryopteris nigropodii, Dryopteris macrophylla, and Dryopteris nigropodii (36).
7	**CN117771286A** (Tianjin University Of Traditional Chinese Medicine)	This publication mentions the application of Terminalia chebula tannic acid and punicalagin in the preparation of therapeutic compositions against SARS-CoV-2, including its Omicron variant. The active monomers, terminalia tannic acid and punicalagin, demonstrated a strong binding force to SARS-CoV-2Mpro (37).
8	**WO2023021479A1** (Alakart Biopharma)	This publication uncovers a synergistic and safe polyherbal formulation for SARS-CoV-2 viral infection comprising essentially Swertia chirata, Zingiber Officinale, Tinospora cordifolia, Justicia adhatoda, Terminalia chebula, and Trichosanthes cucumerina and delivered in a pharmaceutically acceptable neutral agent (38).
9	**WO2023204775A1** (IPMC Group)	This publication unveils a herbal product comprising Saussurea costus root extract for use in treatment comprising a dosage regimen (unit doses of 5 ml to 10 ml) twice a day. This herbal product can be easily manufactured with a simple extraction process and exhibits antiviral activity against COVID-19 disease both in vitro and in vivo (39).
10	**US2023165924A1** (Khushbu Kumari)	This publication describes a herbal formulation for the prevention and management of COVID-19 comprising n-hexane and hydro-alcoholic extracts of Hippophae rhamnoides (90-800 mg/day), and hydro-alcoholic extracts of Tinospora cordifolia (100-500 mg/day) and Occimum sanctum (100-400 mg/day), and the bio-molecules of the said plants regulate the ACE2 receptors in the different organ systems. The formulation may optionally comprise minerals, vitamins, salts, binders, or other known additives. The disclosed formulation exerted antiproliferative, hypolipidemic, anti-atherogenic, antioxidant, and anti-anxiety while reducing homocysteine levels (40).
11	**KR20230085342A** (Dongyang Special Wood)	This publication claims an antiviral composition (nanoemulsion with a diameter of 1 nm to 1 μm) comprising cypress tree extract (20-30 parts by weight) and chlorine dioxide (1000 1800 parts by weight) water prepared from ultra-purified water. The compositions did not exhibit cytotoxicity when exposed to BHK-21 cells (41).
12	**US2023122849A1** (National Research Institute Of Chinese Medicine)	This publication provides a method of treating COVID-19 using a plant composition (NRICM102) comprising Aconitum carmichaelii, Polygonatum odoratum, Poria cocos, Pinellia ternata, Artemisia scoparia, Scutellaria baicalensis, Trichosanthes kirilowii, Magnolia officinalis, Houttuynia cordata, and Glycyrrhiza glabra (42).
13	**KR20230089631A** (The Industry & Academic Cooperation In Chungnam National University)	This publication claims an immune-enhancing pharmaceutical composition for increasing immune activity, comprising antler, aloes, angelica, Cornus officinalis, and spirulina (43).

Discussion

Recent clinical trials have explored the role of many NPs in managing COVID-19 (Figure 1) (15-28).

Figure 1: Recent clinical studies on NPs against COVID-19

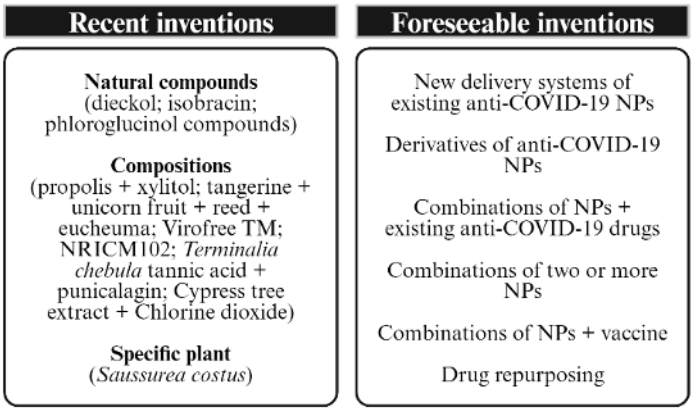


The TOGETHER study in Brazil did not find any significant advantages of spirulina compared to placebo in high-risk COVID-19 patients, even though there were 1126 participants in the experiment (15). Also, the research found anti-inflammatory benefits with a highly absorbable curcumin formulation (curcuRouge®), but it did not affect the advancement of COVID-19 (16). Results from a few experiments are encouraging. A Chinese herbal medication formulation successfully prevented COVID-19 without adverse effects (18), and a curcumin-piperine co-supplementation decreased inflammatory indicators in COVID-19 patients (17). In mild to moderate instances of COVID-19, VCO decreased inflammation and symptoms (19), whereas aromatherapy with thyme oil improved symptoms and vital signs (20). Extracts from Tinospora cordifolia and Adhatoda

vasica, according to research (21), may modulate the immune system and speed up viral clearance. Despite being safe, licorice extract and green propolis did not affect symptom severity and hospital stays, respectively (22,23). These results demonstrate the multifaceted nature of natural product potential and call attention to the necessity for bigger, more controlled studies.

Multiple NPs formulations and compositions with antiviral and immune-boosting potential have been recently patented for use in COVID-19 management (Table 2). These inventions include natural compounds (dieckol; isobracin; phloroglucinol compounds), compositions (propolis + xylitol; tangerine + unicorn fruit + reed + eucheuma; Virofree TM; NRICM102; Terminalia chebula tannic acid + punicalagin; Cypress tree extract + Chlorine dioxide) and specific plant (Saussurea costus). These inventions exert their effects by various mechanisms (Protease 3CLpro; Angiotensin-converting enzyme 2; SARS-CoV-2Mpro) (Table 2). A patent can be granted on many drug-based inventions (44-46) Nonetheless, there is a great deal of room for innovation in the use of NPs in the control of COVID-19. Accordingly, many inventions are foreseeable, including new delivery systems of existing natural anti-COVID-19 drugs, derivatives of plant-derived compounds, new combinations (two or more than two NPs; NPs + existing anti-COVID-19 drugs; NPs + vaccine therapy; NPs + monoclonal antibodies), and drug repurposing of the marketed NPs (Figure 2) (44-50).

Figure 2: Recent and foreseeable inventions on NPs against COVID-19



SARS-CoV-2 continues to spread, although its health effects are becoming more limited and milder in most healthy people. Accordingly, COVID-19 has become a tolerable endemic in many locations after a global pandemic. The endemicity of COVID-19 warrants changing treatment priority from emergency to long-term management (51). NPs, which are safe and immune-modulating, could be used in preventive health regimens, especially in high-risk or resource-limited contexts (8,12). This allows for the study of natural substances as preventative supplements or part of routine wellness programs, especially in populations with limited access to conventional treatments or vaccine reluctance.

Long COVID and post-acute sequelae remain a major issue despite the acute phase of COVID-19 being less dangerous (35). Research on herbal formulations like Virofree™ and Sudarshana cúrna, which reduce inflammation and boost immunity, suggests that NPs could be used to treat or shorten the duration of Long COVID symptoms (26,35). Antioxidants like xanthohumol, immunomodulators like *Withania somnifera*, and anti-inflammatories like curcumin may diminish extended COVID-related systemic inflammation (16,27,28). It is imperative to note that high-quality, focused trials of NPs for extended COVID are still needed. Understanding how NPs minimize cytokine storms, control immunological dysregulation, or improve cellular repair could be helpful.

Finally, to investigate NPs' therapeutic potential in acute and chronic COVID-19, several essential areas might be studied. These areas include mechanical studies, formulation innovations, investigating new medication delivery mechanisms, combination therapies, targeted investigations on antioxidant-rich or adaptogenic NPs for treating long-term COVID and post-viral syndromes, restoring physiological balance, and preventive strategies (44-50).

Conclusion

Natural product use in COVID-19 management has been the subject of several recent clinical research, with mixed or no clear outcomes. Curcumin, licorice, VCO, and Chinese herbal formulations are some of the medications that have shown promise in clinical trials. The inventive application of NPs has been further demonstrated by recent patents that specify formulations intended to cure or prevent COVID-19 and its variations. NPs have the potential to play an increasingly important role in global healthcare to manage COVID-19 as studies continue. Though generally safe, the long-term efficacy and safety of most NPs, particularly when combined with conventional treatments, need extensive clinical confirmation.

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Authors Contribution

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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Data Availability

The datasets generated and/or analysed during the current work are available from the corresponding author upon reasonable request.

References

1. World Health Organization. Coronavirus disease (COVID-19) pandemic. Available at https://www.who.int/emergencies/diseases/novel-coronavirus-2019 (Accessed on January 6, 2025)
2. World Health Organization. WHO COVID-19 dashboard. https://data.who.int/dashboards/covid19/cases (Accessed on January 6, 2025)
3. Mawazi SM, Fathima N, Mahmood S, Al-Mahmood SMA. Antiviral therapy for COVID-19 virus: A narrative review and bibliometric analysis. Am J Emerg Med. 2024; 85: 98-107.
4. Chandra H, Yadav A, Prasad R, Sagar K, Bhardwaj N, Kumar Gupta K, Singh Thakur G, Nigam M, Pezzani R, Paulo Martins de Lima J, Douglas Melo Coutinho H, Prakash

Mishra A. COVID 19: Prevention and treatment through the Indian perspective. Cytokine. 2024; 183: 156756.

5. Akpoviroro O, Sauers NK, Uwandu Q, Castagne M, Akpoviroro OP, Humayun S, Mirza W, Woodard J. Severe COVID-19 infection: An institutional review and literature overview. PLoS One. 2024; 19(8): e0304960.
6. Ketebchi S, Papari Moghadamfard M. A review on the effective natural compounds of medicinal plants on the COVID-19. Nat Prod Res. 2024: 1-14.
7. Mohammed MA. Fighting cytokine storm and immunomodulatory deficiency: By using natural products therapy up to now. Front Pharmacol. 2023; 14: 1111329.
8. Almuqbil M, Alshaikh S, Alrumayh N, Alnahdi F, Fallatah E, Almutairi S, Imran M, Kamal M, Almehmadi M, Alsaiari AA, Alqarni WAA, Alasmari AM, Alwarthan S, Rabaan AA, Almadani ME, Asdaq SMB. Role of Natural Products in the Management of COVID-19: A Saudi Arabian Perspective. Healthcare (Basel). 2023; 11(11): 1584.
9. Imran M, Thabet HK, Alaqel SI, Alzahrani AR, Abida A, Alshammari MK, Kamal M, Diwan A, Asdaq SMB, Alshehri S. The Therapeutic and Prophylactic Potential of Quercetin against COVID-19: An Outlook on the Clinical Studies, Inventive Compositions, and Patent Literature. Antioxidants (Basel). 2022; 11(5): 876.
10. Imran M, Khan SA, Abida, Alshammari MK, Alkhaldi SM, Alshammari FN, Kamal M, Alam O, Asdaq SMB, Alzahrani AK, Jomah S. *Nigella sativa* L. and COVID-19: A Glance at The Anti-COVID-19 Chemical Constituents, Clinical Trials, Inventions, and Patent Literature. Molecules. 2022; 27(9): 2750.
11. Chen J, Ding Z. Advances in natural product anti-coronavirus research (2002-2022). Chin Med. 2023; 18(1): 13.
12. Liu ZQ. How many organic small molecules might be used to treat COVID-19? From natural products to synthetic agents. Eur J Med Chem. 2024; 278: 116788.
13. Chen XY, Lu CL, Wang QY, Pan XR, Zhang YY, Wang JL, Liao JY, Hu NC, Wang CY, Duan BJ, Liu XH, Jin XY, Hunter J, Liu JP. Traditional, complementary and integrative medicine for fatigue post COVID-19 infection: A systematic review of randomized controlled trials. Integr Med Res. 2024; 13(2): 101039.
14. Gasmi A, Noor S, Dadar M, Semenova Y, Menzel A, Gasmi Benahmed A, Bjørklund G. The Role of Traditional Chinese Medicine and Chinese Pharmacopoeia in the Evaluation and Treatment of COVID-19. Curr Pharm Des. 2024; 30(14): 1060-1074.
15. Reis G, Augusto Dos Santos Moreira Silva E, Carla Medeiros Silva D, Thabane L, Santiago Ferreira T, Vitor Quirino Dos Santos C, Paula Figueiredo Guimaraes Almeida A, Cançado Monteiro Savassi L, Dias de Figueiredo Neto A, Lanna França Reis L, Helena de Souza Campos V, Bitarães C, Diniz Callegari E, Izabel Campos Simplicio M, Barra Ribeiro L, Oliveira R, Harari O, Forrest JI, Lat PK, Dron L, Thorlund K, Mills EJ. Effect of spirulina on risk of hospitalization among patients with COVID-19: the TOGETHER randomized trial. Am J Clin Nutr. 2024; 120(3): 602-609.
16. Kishimoto A, Komiyama M, Wada H, Satoh-Asahara N, Yamakage H, Ajiro Y, Aoyama H, Katsuura Y, Imaizumi A, Hashimoto T, Sunagawa Y, Morimoto T, Kanai M, Kakeya H, Hasegawa K. Efficacy of highly bioavailable oral curcumin in asymptomatic or mild COVID-19 patients: a double-blind, randomized, placebo-controlled trial. J Health Popul Nutr. 2024; 43(1): 93.
17. Askari G, Bagherniya M, Kiani Z, Alikiaii B, Mirjalili M, Shojaei M, Hassanizadeh S, Vajdi M, Feizi A, Majeed M, Sahebkar A. Evaluation of Curcumin-Piperine Supplementation in COVID-19 Patients Admitted to the Intensive Care: A Double-Blind, Randomized Controlled Trial. Adv Exp Med Biol. 2023; 1412: 413-426.
18. Du P, Lam WC, Leung C, Li H, Lyu Z, Yuen CS, Cheung CH, Lam TF, Bian Z, Zhong L. Efficacy and safety of Chinese herbal medicine to prevent and treat COVID-19 household close contacts in Hong Kong: an open-label, randomized controlled trial. Front Immunol. 2024; 15: 1359331.
19. Angeles-Agdeppa I, Nacis JS, Dayrit FM, Tanda KV. Virgin coconut oil (VCO) supplementation relieves symptoms and inflammation among COVID-19 positive adults: a single-blind randomized trial. J Nutr Sci. 2024; 13:e5.
20. Öner U, Cengiz Z. The effects of aromatherapy with thyme oil on disease symptoms, vital findings, and hemodynamic parameters in COVID-19 patients. Explore (NY). 2024; 20(4): 544-553.
21. Verma M, Rawat N, Rani R, Singh M, Choudhary A, Abbasi S, Kumar M, Kumar S, Tanwar A, Misir BR, Khanna S, Agrawal A, Faruq M, Rai S, Tripathi R, Kumar A, Pujani M, Bhojani M, Pandey AK, Nesari T, Prasher B. Adhatoda vasica and Tinospora cordifolia extracts ameliorate clinical and molecular markers in mild COVID-19 patients: a randomized open-label three-armed study. Eur J Med Res. 2023; 28(1): 556.
22. Silveira MAD, Menezes MA, de Souza SP, Galvão EBDS, Berretta AA, Caldas J, Teixeira MB, Gomes MMD, Damiani LP, Bahiense BA, Cabral JB, De Oliveira CWLM, Mascarenhas TR, Pinheiro PCG, Alves MS, de Melo RMV, Leite FM, Nonaka CKV, Souza BSF, Baptista NU, Teles F, da Guarda SF, Mendes AVA, Passos RDH. Standardized Brazilian green propolis extract (EPP-AF®) in COVID-19 outcomes: a randomized double-blind placebo-controlled trial. Sci Rep. 2023; 13(1): 18405.
23. Ameri A, Farashahinejad M, Davoodian P, Safa O, Kusha A, Dadvand H, Hassanipour S, Fathalipour M. Efficacy and safety of licorice (Glycyrrhiza glabra) in moderately ill patients with COVID-19: a randomized controlled trial. Inflammopharmacology. 2023; 31(6): 3037-3045.
24. Yousefi M, Sadriirani M, Mahmoodi S, Samimi B, Pourmahmoudi A, Hosseinikia M, Sadeghi O, Roustaei N, Saeedinezhad Z, Espín JC, Ansari S, Panahande SB. Adjuvant pomegranate juice intake improves the inflammatory status of hospitalized COVID-19 patients: A randomized and placebo-controlled trial. Complement Ther Med. 2023; 75: 102958.
25. Chopra A, Tillu G, Chuadhary K, Reddy G, Srivastava A, Lakdawala M, Gode D, Reddy H, Tamboli S, Saluja M, Sarmukaddam S, Gundeti M, Raut AK, Rao BCS, Yadav B, Srikanth N, Patwardhan B. Co-administration of AYUSH 64 as an adjunct to standard of care in mild and moderate COVID-19: A randomized, controlled, multicentric clinical trial. PLoS One. 2023; 18(3): e0282688.

26. Wijewickrama A, Idampitiya D, Karunarathne M, Pahalagamage S, Sellahewa K, Govindapala D, Kalambarachchi H, Sooriyarachchi R, Chandrarathne N, Goonaratna C, Perera J. Efficacy and safety of Link Natural Sudarshana, an Ayurvedic herbal preparation in COVID-19 patients: A phase II multicenter double-blind randomized placebo-controlled trial. J Ethnopharmacol. 2024; 323: 117535.

27. Singh H, Yadav B, Rai AK, Srivastava S, Saiprasad A, Jameela S, Singhal R, Muralidharan S, Mohan R, Chaudhary S, Rana R, Khanduri S, Sharma BS, Chandrasekhararao B, Srikanth N, Dhiman KS. Ashwagandha (Withania somnifera) and Shunthi (Zingiber officinale) in mild and moderate COVID-19: An open-label randomized controlled exploratory trial. Complement Ther Med. 2023; 76: 102966.

28. Dabrowski W, Gagos M, Siwicka-Gieroba D, Piechota M, Siwiec J, Bielacz M, Kotfis K, Stepulak A, Grzycka-Kowalczyk L, Jaroszynski A, Malbrain ML. Humulus lupus extract rich in xanthohumol improves the clinical course in critically ill COVID-19 patients. Biomed Pharmacother. 2023; 158: 114082.

29. Kheirandish E, Mahdizadeh M, Mahdizadeh M, Rezaeitalab F, Yousefi M, Shojaee SSR. Investigating the effect of echinacea extraction syrup on the outcomes of lower respiratory infections in patients with COVID-19: a randomized clinical trial study. Virol J. 2024; 21(1): 319.

30. Ameri A, Farashahinejad M, Davoodian P, Safa O, Hassaniazad M, Parsaii M, Heidari B, Hassanipour S, Akhlaghi B, Fathalipour M. The efficacy and safety of ginger (Zingiber officinale) rhizome extract in outpatients with COVID-19: A randomized double-blind placebo-control clinical trial. Medicine (Baltimore). 2024; 103(22): e38289.

31. Veronneau J. Formulation for the prevention and/or treatment of COVID-19. United States Patent Application Publication Number US2024115622A1. 2024. Available at https://patents.google.com/patent/US20240115622A1/en?oq=US2024115622A1.

32. Yim SK, Kang SM, Tark DS, Lee GH, Song BM, Han HJ, Yang JH, Gu HJ, Lee EG. Composition for ameliorating, preventing or treating viral infectious disease comprising dieckol as active ingredient. PCT Patent Application Publication Number WO2024135941A1. 2024. Available at https://patents.google.com/patent/WO2024135941A1/en?oq=WO2024135941A1.

33. Wei D, Khan A, Wang H. New application of isobrazilin to inhibition of COVID-19 infection. Chinese Patent Application Publication Number CN115837020A. 2023. Available at https://patents.google.com/patent/CN115837020A/en?oq=CN115837020A.

34. Sun Y. Plant extracting solution and application thereof in preparation of novel coronavirus resisting medicine. Chinese Patent Application Publication Number CN117045752A. 2023. Available at https://patents.google.com/patent/CN117045752A/en?oq=CN117045752A.

35. Duan M, Yun H, Huang Z, Li J, Ruan S. Methods and compositions for preventing and treating severe special infectious pneumonia (COVID-19) and long-term severe special infectious pneumonia (LONG COVID). Chinese Patent Application Publication Number CN117957009A. 2024. Available at https://patents.google.com/patent/CN117957009A/en?oq=CN117957009A.

36. Hou B, Bai T, Zhang R, Chen X, Ni G, Zhou T, Lin Z, Zhu H. Application of phloroglucinol compound in preparation of coronavirus 3CLpro target protein inhibitor and preparation method of phloroglucinol compound. Chinese Patent Application Publication Number CN118045073A. 2024. Available at https://patents.google.com/patent/CN118045073A/en?oq=CN118045073A.

37. Zhang M, Zhang J, Wang Y, Yu H, Wu H, Liu L. Application of fructus chebulae and active monomer thereof in preparation of products for inhibiting novel coronavirus and resisting Armike virus. Chinese Patent Application Publication Number CN117771286A. 202). Available at https://patents.google.com/patent/CN117771286A/en?oq=CN117771286A.

38. Reddy R, Muthu H. A synergistic poly herbal formulation for treating viral infections and a process of preparation thereof. PCT Patent Application Publication Number WO2023021479A1. 202). Available at https://patents.google.com/patent/WO2023021479A1/en?oq=WO2023021479A1.

39. Al-Zendani MAA, Al-Zendani AAH. Herbal product for use in the prevention and/or treatment of COVID-19. PCT Patent Application Publication Number WO2023204775A1. 2023. Available at https://patents.google.com/patent/WO2023204775A1/en?oq=WO2023204775A1.

40. Dubey GP, Agrawal N, Agrawal P, Ramkumar KM, Kunka M, Satishkumar RC, Saini RG, Dubey R. Herbal Formulation for the Prevention and Management of COVID-19 by Regulating Immunomodulatory Properties. United States Patent Application Publication Number US2023165924A1. 2023. Available at https://patents.google.com/patent/US20230165924A1/en?oq=US2023165924A1.

41. Lee SY. Antiviral composition comprising natural product-derived substance and chlorine dioxide solution. Korean Patent Application Publication Number KR20230085342A. 2023. Available at https://patents.google.com/patent/KR20230085342A/en?oq=KR20230085342A.

42. Su Y, Chiou W, Shen Y, Wei W, Tsai K, Liao C, Tseng Y, Chiou C, Lin Yu, Wang L, Huang C, Lin C, Lin C, Huang Y, Lin C, Lin J, Yang Y, Chiu C, Cheng S, Kuo H, Lin W, Lin C, Lai B, Hsu Y, Tsai T, Hsu W, Fong T, Huang Y, Tsai C, Yang Y, Tsai M, Cheng M, Huang S. Use of plant composition, traditional Chinese medicine composition in preparing medicine for treating COVID-19. United States Patent Application Publication Number US2023122849A1. 2023. Available at https://patents.google.com/patent/US20230122849A1/en?oq=US2023122849A1.

43. Kang JS, Kim YH, Cho CW, Lee YS, Hwang IK. Composition of herbal medicine mixture with the enhanced immune activity. Korean Patent Application Publication Number KR20230089631A. 2023. Available at https://patents.google.com/patent/KR20230089631A/en?oq=KR20230089631A.

44. Imran M, Alshrari AS, Thabet HK, Abida, Afroz Bakht M. Synthetic molecules as DprE1 inhibitors: A patent review. Expert Opin Ther Pat. 2021; 31(8): 759-772.

45. Imran M, Alshrari AS, Asdaq SMB, Abida. Trends in the development of remdesivir based inventions against COVID-19 and other disorders: A patent review. J Infect Public Health. 2021; 14(8): 1075-1086.

46. Imran M, Khan SA, Abida, Alshrari AS, Eltahir Mudawi MM, Alshammari MK, Harshan AA, Alshammari NA. Small molecules as kinetoplastid specific proteasome inhibitors for leishmaniasis: a patent review from 1998 to 2021. Expert Opin Ther Pat. 2022; 32(5): 591-604.

47. Imran M, Abida, Alotaibi NM, Thabet HK, Alruwaili JA, Eltaib L, Alshehri A, Alsaiari AA, Kamal M, Alshammari AMA. Repurposing Anti-Dengue Compounds against Monkeypox Virus Targeting Core Cysteine Protease. Biomedicines. 2023; 11(7): 2025.

48. Imran M, Abida, Alotaibi NM, Thabet HK, Alruwaili JA, Eltaib L, Alshehri A, Kamal M. Investigation of natural compounds as methyltransferase inhibitors against dengue virus: an *in silico* approach. J Biomol Struct Dyn. 2024: 1-16.

49. Asdaq SMB, Rabbani SI, Alkahtani M, Aldohyan MM, Alabdulsalam AM, Alshammari MS, Alajlan SA, Binrokan A, Mohzari Y, Alrashed A, Alshammari MK, Imran M, Nayeem N. A Patent Review on the Therapeutic Application of Monoclonal Antibodies in COVID-19. Int J Mol Sci. 2021; 22(21): 11953.

50. Alshrari AS, Hudu SA, Imran M, Asdaq SMB, Ali AM, Rabbani SI. Innovations and development of COVID-19 vaccines: A patent review. J Infect Public Health. 2022; 15(1): 123-131.

51. Cohen LE, Spiro DJ, Viboud C. Projecting the SARS-CoV-2 transition from pandemicity to endemicity: Epidemiological and immunological considerations. PLoS Pathog. 2022; 18(6):e1010591.

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