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REVIEW ARTICLE

Exploring Phytotherapy's Preventive and Therapeutic Impact on Global COVID-19 Management: A Narrative Review

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Abstract:

Introduction:

The WHO Emergency Committee advocates preventive strategies for COVID-19 management, emphasising vaccines as highly effective but acknowledging their limitations. Chloroquine and hydroxychloroquine, initially effective against COVID-19, were discontinued due to severe side effects. Further clinical trials are imperative to establish the safety and efficacy of new antiviral agents, some of which may have harmful effects on human development.

Objectives:

The shortcomings of various conventional treatments have prompted urgent efforts to discover safe, natural compounds that may be useful in combating COVID-19. This study aims to review research that has investigated the potential of traditional phytotherapies used by different populations for the prevention and symptomatic treatment of COVID-19 infection.

Methods:

This paper reviewed scientific studies published through searching on search engines such as PubMed, Scopus, Google Scholar, ScienceDirect and Elsevier from May until October 2023.

Results:

The preventive and anti-COVID-19 attributes of Traditional Chinese Medicine, Ayurvedic formulations and African medicinal plants have been substantiated in research. In Nepal, recommendations endorse the utilisation of medicinal plants for herbal teas and homemade sanitizers. *Zingiber officinale*, *Curcuma longa L*. and *Curcuma xanthorriza Roxb*., along with *Camellia sinensis* are crucial Indonesian medicinal plants with potential for treating COVID-19. *Z. officinale* was predominantly chosen for relieving coughs and sore throats associated with COVID-19 in Saudi Arabia.

Discussion:

The immunomodulatory properties of medicinal plants, which may prove useful in combating COVID-19, have been verified *via* elevation of the level of peripheral WBCs, IgM, IgG; inhibition of leukotrienes and prostaglandins, maintenance of the integrity of intestinal mucosal barrier and regulation of HMGB1. The antiviral effects of herbs, including the inhibition of viral DNA and RNA replication, down-regulation of oxidative stress, and the impediment of SARS-CoV-2 access to vascular endothelial cells, suggest their potential to facilitate earlier recovery from COVID-19 infection.

Conclusion:

Advancing scientific research in phytotherapy promises the possibility of novel approaches for effectively managing future infectious diseases and pandemics.

Keywords: Preventive, Immunomodulatory, Therapeutic, Phytotherapy, COVID-19, SARS-CoV-2.

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1. INTRODUCTION

Respiratory tract infections (RTIs) mainly involve the upper respiratory tract and occur most frequently in children and the elderly. While a variety of viruses may cause RTIs, there is evidence of concurrent bacterial pathogens in viral respiratory infections [1, 2]. The emergence of COVID-19, stemming from Wuhan, Hubei Province, China, attributed to the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), evolved into a global pandemic due to its rapid

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airborne transmission [3, 4]. On May 5, 2023, the World Health Organization (WHO) Emergency Committee on COVID-19 declared the disease no longer constituted a Public Health Emergency of International Concern (PHEIC). However, the WHO still advocates measures for its control and management [5, 6]. Ogunrinola *et al.* [4] argue that non-therapeutic measures (like masks, handwashing, social distancing, and lockdowns) have proven inadequate in many developing nations. Amidst the pandemic, efforts have focused on preventive strategies, yet educating people on the rationale behind these strategies remains crucial [7]. However, population-level immunity has increased significantly on a global scale, WHO SAGE (Strategic Advisory Group of Experts on Immunization) advocates the development of novel approaches to COVID-19 vaccine administration [8]. Despite vaccines being recognized as highly effective in disease prevention, they have limitations. Evidence suggests a reduced duration of protection conferred by vaccines, including primary series and booster doses, against SARS-CoV-2 infections, hospitalizations, and mortality. The emergence of new virus variants intensifies the urgency for effective vaccines, compounded by concerns over vaccine side effects. Additionally, certain variants, like Omicron, challenge vaccine efficacy, necessitating complementing measures such as mask-wearing and physical distancing for optimal effectiveness [9, 10]. Conventional therapeutic strategies against COVID-19 involve interventions targeting various aspects and stages of the disease, including viral growth and proliferation. Although chloroquine and hydroxychloroquine were known as effective drugs for reducing the risk of mortality and morbidity associated with COVID-19 through various antiviral mechanisms of action, their routine use was discontinued due to serious side effects. While the *in vitro* antiviral properties of Lopinavir-Ritonavir and Ivermectin have been established, more clinical trials are necessary to prove the safety and efficacy of these agents in COVID-19 patients. Favipiravir is another potent antiviral drug that possesses potential teratogenic and embryotoxic properties in humans [4, 11, 12]. The shortcomings of various conventional treatments have led to urgent efforts to discover safe, natural compounds that may be useful in combating COVID-19. Medicinal plants are a source of bioactive compounds which represent pharmacological effects. Moreover, medicinal plants with immune-enhancing properties, along with phytochemicals and bioactive immunoadjuvants, stimulate immunity through diverse mechanisms, which plays a pivotal role in their ability to prevent disease. Although traditional medicines are not risk-free, the application of their metabolites and extracts for diseases such as cancer, diabetes, hypoglycemia, hypertension, asthma, cardiovascular diseases, as well as COVID-19-associated lung infections are areas of research that are gathering interest globally. The well-established role of traditional medicine in the maintenance of health, illness prevention, and treatment has prompted the WHO to support the standardisation of natural products to improve their safety and quality [13 - 16]. This narrative review aims to provide an overview of the latest research investigating the potential of traditional phytotherapies used by different populations for the prevention and symptomatic treatment of COVID-19 infection.

2. METHODOLOGY

2.1. Sources of Information

Peer-reviewed, and published scientific studies were selected using academic search engines such as PubMed, Scopus, Google Scholar, ScienceDirect and Elsevier between May and October 2023. Studies published from 2019 to 2023 were selected as recent advances in the field. Additionally, in order to complement the search, a reference list of relevant reports was checked.

2.2. Search Terms

Manual searches were conducted independently by reviewers. We employed a multi-query search strategy using terms such as 'COVID-19' or 'SARS-CoV-2' or 'novel coronavirus' and 'Traditional Chinese Medicine' or 'Ayurveda' or 'phytotherapy' or 'medicinal plants' or 'randomised controlled trial'.

2.3. Selection Criteria

Inclusion criteria were limited to original, high-quality papers in English focusing on the application of different medicinal plants and phytochemicals in the context of COVID-19 worldwide, based on *in vivo*, *in vitro*, *in silico,* clinical trials, meta-analysis, questionnaire surveys, technical reports and narrative reviews on herbal drugs. Exclusion criteria were identified considering items such as old data, inappropriate topics, case reports, study protocols and letters to editors. The scope of this review is limited to the usage of medicinal plants exclusively. Therefore, studies examining phytotherapy in combination with various types of complementary and alternative medicine (CAM) interventions were excluded.

2.4. Risk of Bias Assessment

The quality of the studies and reviews included may potentially influence the outcomes of our study.

3. RESULTS

3.1. Study Selection Process

The outcomes of the search process are depicted in Fig. (**1**). Initially, 984 papers were identified, with 878 duplicates subsequently removed. Screening for eligibility reduced the records to 429. Eventually, 20 articles aligned with the inclusion criteria for this review [17].

The selected articles underwent comprehensive analysis, with particular regard to both preventive and treatment approaches for COVID-19 in various countries. The focus was on the application of indigenous herbs or herbal formulations of various origins. Recent literature was incorporated to establish a scientific basis and explore the mechanisms of action associated with commonly utilised medicinal plants.

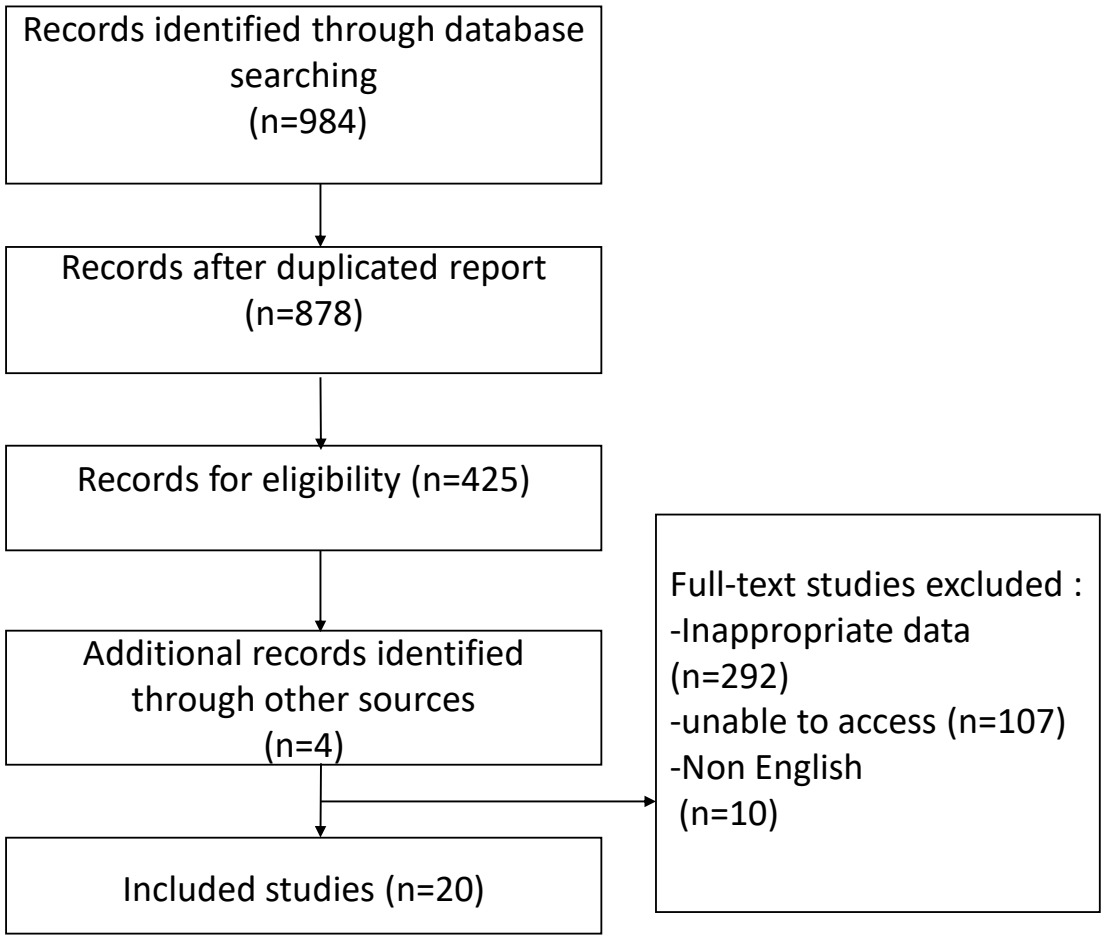

Fig. (1). Flow chart for the literature selection process.

4. DISCUSSION

4.1. Preventive Use of Medicinal Plants

The increasing prevalence of viral respiratory infections and major epidemics underscores the need for governments to develop intricate, effective strategies to safeguard their populations [7]. While traditional preventive measures depend on understanding virus characteristics and transmission patterns, enhancing immune responses through immuno modulatory agents holds promise for pre-exposure protection against viral respiratory infections like COVID-19 [18]. The limitations of conventional immunomodulators have steered attention toward natural agents in preventive medicine. Traditional Chinese Medicines (TCM) have demonstrated regulatory effects on the immune system by modulating immune cells and cytokines [19].

4.1.1. Immunoregulatory Properties of TCM

TCM's antiviral properties extend beyond direct virus inhibition, encompassing immune regulation. Herbs like *Astragalus, Salvia*, *Acanthopanax senticosus* and *Gentiana* induce interferon and immunoglobulin production, showcasing their antiviral potential. Through an *in vivo* assay, Li and colleagues examined the immunomodulatory properties of water ingredient extract (WIE) of *Astragalus,* which contains biologically active substances such as polysaccharides, saponins, astragaloside IV and flavonoids. Intragastric administration of WIE (1 g herb/kg/per day/for 18 days) in mice elevated the number of peripheral white blood cells (WBC), serum levels of IgG and IgM immunoglobulins, both T and B lymphocyte proliferations and natural killer (NK) cell activity. Additionally, TCM utilises traditional aromatherapy methods with herbs such as *Atractylodes lanceolata*, *Phellodendron amurense*, and *Artemisia argyi* for preventive purposes [20, 21].

4.1.2. Preventive Effects of TCM against COVID-19 through Interactions with Gut Microbiota

The intestinal mucosal barrier provides immune responses against potentially harmful substances such as dietary antigens and microbial agents. On the one hand, the intestinal microbiome has been suggested as one of the regulatory factors of immune homeostasis; on the other hand, there is a relationship between SARS-CoV-2 and gut microbiota in such a way as to bind to angiotensin-converting enzyme 2 (ACE2) receptor on the surface of intestinal epithelial cells. This can lead to alterations of the gut microbiota, reduction of mucosal barrier immunity, endotoxemia and formation of inflammatory

storm in COVID-19 patients. The single Chinese medicines *Ginseng radix et rhizoma*, berberine, *Lonicerae japonicae flos*, *Rehmanniae radix praeparata*, *Artemisiae argyi folium* and Qingfei Paidu decoction regulate gut microbiota structure. Therefore, TCM may play an important role in preventing novel coronavirus disease through interactions with gut microbiota and modulating the pharmacological effects of phytochemicals. In addition, *Rhei radix et rhizome* and *Ganoderma lucidum* have been reported to maintain and protect the integrity of the intestinal mucosal barrier [22 - 24].

4.1.3. Immunomodulatory Properties of Medicinal Plants in Northeast Asia

Babich and colleagues conducted a review focusing on medicinal plants prevalent in Northeast Asia, known for their beneficial impact on lung health and immune system fortification. Among these, Andrographolide, a derivative of *Andrographis paniculata*, showcases properties in reducing inflammatory cytokine levels, augmenting immune response, modulating NK cell activity, and fostering the formation of cytotoxic T lymphocytes. Curcumin, the primary phytochemical constituent of *Curcuma longa L*., inhibits leuko trienes and prostaglandins while enhancing nitric oxide (NO) and interleukins (IL-2, IL-6, IL-10, IL-12), Interferon-gamma (IFN-γ), and Tumor Necrosis Factor (TNF-α). Notably, Curcumin targets the regulation of high mobility group box 1 (HMGB1), suppressing HMGB1-mediated pro-inflammatory responses. HMGB1 is associated with inducing ACE2 receptor expression, a factor in SARS-CoV-2 pathogenesis. Curcumin has been observed to down-regulate ACE2 expression, potentially mitigating SARS-CoV-2 infection [25 - 27]. However, since curcumin has been shown to alter some pharmacokinetic parameters of conventional medications (potential curcumin-drug interaction), concomitant use of curcumin with conventional drugs requires close observation [28].

4.1.4. Preventive Medicinal Plants against COVID-19 in Nepal

The Government of Nepal's Ministry of Health & Population advocates the use of specific medicinal plants like *Curcuma longa*, *Cuminum cyminum L*. and *Allium sativum* in routine cooking practices. Additionally, mustard oil is recommended for nasal application (1 tablespoonful/in both nostrils/twice a day) or as a mouthwash (1 tablespoonful/swish in the mouth for 2 to 3 minutes), while a decoction of tulsi (*Ocimum tenuiflorum*), *Cinnamomum*, *Piper nigrum* and *Zingiber officinale* serves as herbal tea (Kadha). There are different Ayurvedic methods to prepare Kadha. The most common ingredients and their quantity to prepare the decoction have been discussed by Khemariya *et al*. [29]. Homemade sanitizer preparations involve a mixture of neem, tulsi, aloe, artemisia leaves, and dry garlic [30]. *Cuminum cyminum* polysaccharide (191.4-512.2 × 103 g/mol) exhibits immune-stimulatory properties by inducing RAW264.7 macrophage proliferation through the activation of Nuclear factor kappa-B (NF-κB) and mitogen-activated protein kinases (MAPKs) signalling pathways. This activation leads to the release of NO and the expression of inflammatory cytokines like TNF-α, IL-1β, IL-6, and IL-12. Furthermore, these polysaccharides activate NK-92 cells, enhancing the production of TNF-α and IFN-γ [31].

4.1.5. The Preventive Role of Ayurvedic Medicine against COVID-19

The use of nasal sprays and oropharyngeal solutions for reducing viral load in the upper respiratory tract has emerged as an effective preventive measure due to the highly transmissible nature of the novel coronavirus through respiratory droplets. Ayurvedic medicine recommends such preventive regimens during epidemics. Docking analysis has indicated an Ayurvedic formulation containing *Citrus medica* and *Zingiber officinale*, comprising various phytochemicals. These compounds demonstrate an affinity to the ACE-2 receptor binding site of the SARS-CoV-2 spike glycoprotein, potentially inhibiting its action. The phytochemicals associated with this effect include rhoifolin, naringin, neohesperidin, apigenin 6,8-di-C-glucoside, adenine, hesperidin, 6-gingerol, xanthin, 8-gingerol, scopoletin, isovanillin, 10-gingerol, 10-shogaol, 8-paradol, and 10-paradol. Utilising these compounds in medicinal preparation as a nasal airway cleanser could potentially prevent disease or reduce the severity of COVID-19 [32, 33]. However, the results of *in vitro* and *in vivo* experiments conducted by Lu and coauthors [34] demonstrated that 8-gingerol (up to 100 μg/ml/for 24 hours) did not cause a toxic effect on mice splenocytes, concluding that the reason was related to the immunosuppressive property of 8-gingerol. Furthermore, this constituent of *Z. officinale,* dependent on dose (25, 50, 100 mg/kg), markedly decreased $CD3^+$ $CD19^+$ cells while significantly suppressing $CD3^+$ T cells at 100 mg/kg in ovalbumin (OVA)-immunised mice. Moreover, the administration of 8-gingerol revealed a significant reduction in serum IgG1 and IgG2b levels at doses 50, 100 mg/kg and 100 mg/kg, respectively, in OVA-immunised mice. The dual immunomodulatory properties of ginger, therefore, remain a matter of controversy.

4.1.6. Nigerian Immunomodulatory Medicinal Plants

Nigerian healers advocate immune-boosting measures involving garlic (*Allium sativum*), guava leaves (*Psidium guajava*), lemongrass *(Cymbopogon citratus*) and cinnamon (*Cinnamomum zeylanicum*) [35]. The immunomodulatory properties of *Cymbopogon citratus (LG)* have been examined by Bachiega and Sforcin [36]. LG extract (100 g/well) demonstrated an anti-inflammatory effect *via* the inhibition of IL-6 production by macrophage cells. The same dose of LG inhibited IL-6 and IL-10 in LPS-incubated macrophage cells of BALB/c mice, probably through inhibiting NF-κB.

Table **1** summarises a list of commonly used medicinal plants with potential preventive effects against COVID-19. The immunomodulatory activity of various types of medicinal plants against COVID-19 is summarised in Fig. (**2**).

4.2. Therapeutic Effects of Medicinal Plants

4.2.1. Therapeutic Effects of CHM Formulas for COVID-19

The use of Chinese herbal medicine (CHM) to address acute infectious conditions has a longstanding history. Randomised controlled trials (RCTs) have demonstrated the efficacy of certain CHM formulas, whether used alone or combined with conventional pharmacotherapy, in managing

Table 1. Commonly utilised medicinal plants with potential preventative properties against COVID-19.

China (TCM) [21, 22]	Ayurveda (India) [33]	Northeastern Asia [25]	Nepal [29]	Nigeria [35]
Atractylodes lanceolata (aromatherapy, decoction)	*Citrus medica*	*Andrographis paniculata* (aqueous or ethanol extract)	*Curcuma longa*	*Allium sativum*
Phellodendron amurense (aromatherapy, decoction)	*Zingiber officinale*	*Curcuma longa L.* (aqueous or ethanol extract)	*Cuminum cyminum L.*	*Psidium guajava*
Astragalus	-	*Echinacea purpurea* (syrup, ethanol extract, sap)	*Allium sativum*	*Cymbopogon citratus*
Ginseng radix et rhizoma	-	*Rhodiola rosea* (aqueous extract)	*Mustard oil*	*Cinnamomum zeylanicum*
Berberine	-	*Saposhnikovia divaricata* (ethanol extract)	*Ocimum tenuiflorum* (decoction)	-
Lonicerae japonicae flos (decoction)	-	-	*Cinnamomum* (decoction)	-
Rehmanniae radix praeparata	-	-	*Piper nigrum* (decoction)	-
Artemisiae argyi folium (decoction)	-	-	*Zingiber officinale* (decoction)	-
Salvia	-	-	-	-

Note: Prepared forms of medicinal plants are mentioned according to their availability in the papers referred to in the main text.

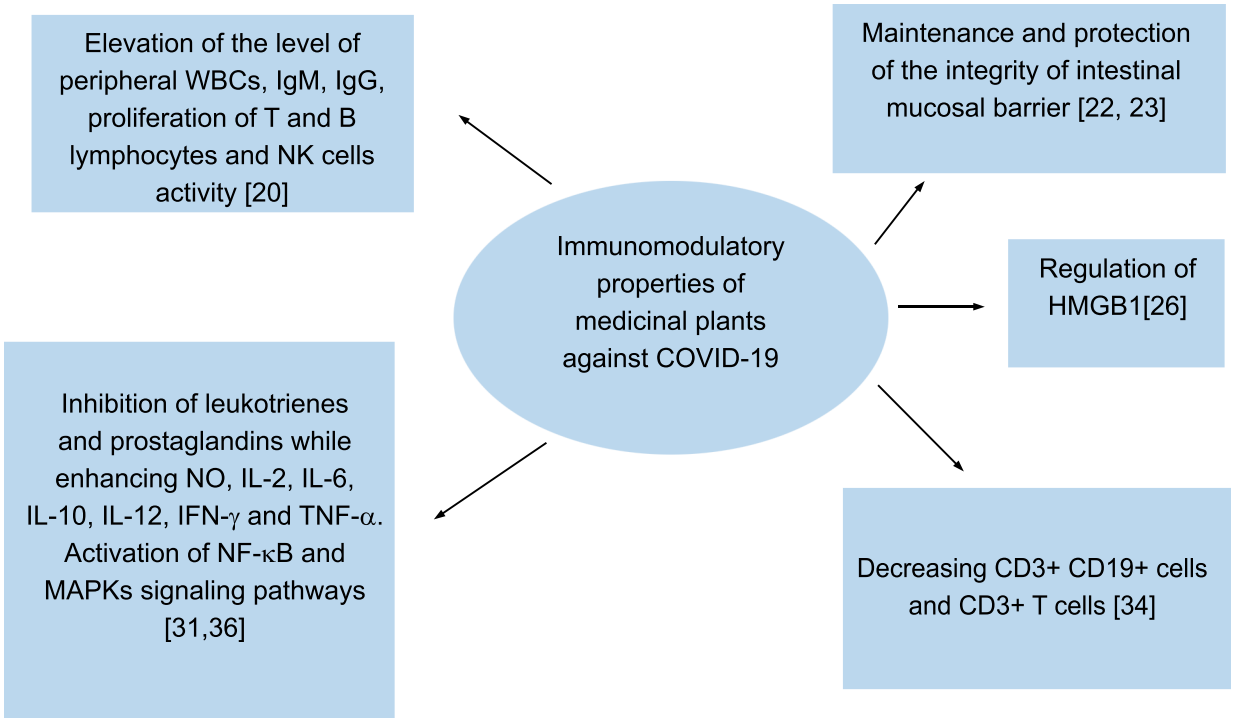

Fig. (2). Immunomodulatory activity of various types of medicinal plants against COVID-19.

various stages of COVID-19 [37]. These formulas exhibit dual functionality: some active compounds within them display antiviral activity by suppressing viral replication through targeted signalling pathways associated with a viral infection. Simultaneously, they reduce apoptosis and aid in repairing body damage caused by coronavirus infection by enhancing nuclear receptor activity signalling pathways, potentially proving effective in COVID-19 treatment [38]. Among these formulations, the Lianhua Qingwen (LQ) capsule, containing 13 herbs (Table **2**), stands out as one of the most extensively studied preparations for treating COVID-19 [39]. The preventive and therapeutic roles of this formula in addressing the novel global pandemic have been investigated through *in vivo* research, clinical trials, and meta-analyses. An updated meta-analysis encompassing 916 participants conducted by Li and colleagues demonstrated that combining LQ various

regimens (4 pieces/three times daily (Tid)/10 days; 4 capsules/Tid/14 days; 1 bag/Tid; 6 g/Tid/7 days) with conventional treatments significantly improves clinical symptoms, reduces adverse events, shortens fever duration in hospitalised patients, improves chest CT findings, and decreases the risk of progression to severe cases [40]. Furthermore, an ongoing randomised, double-blind, placebo-controlled international multicenter trial involving China, Cambodia, Thailand, Vietnam, and Singapore aims to comprehensively evaluate LQ's therapeutic characteristics (1.4 g/Tid/14 days), specifically targeting the improvement of primary symptoms, respiratory issues, gastrointestinal issues, and systemic manifestations of the disease [41]. Xuanfei Baidu decoction, a newly formulated Traditional Chinese Medicine (TCM) prescription for COVID-19, comprises 13 herbs (Table **2**). These herbs collectively exhibit antiviral, anti-inflammatory, antioxidative, antibacterial, and antifungal properties. This unique composition (150 ml/twice daily/14 days; 200 ml/twice per day/7 days) is designed to ameliorate clinical symptoms, reduce hospitalisation duration, prevent symptom exacerbation and consequently lower mortality rates [42].

4.2.2. Therapeutic Effects of Ayurvedic Formulations for COVID-19

The anti-inflammatory potential of Ayurvedic formulations has been extensively investigated through various studies encompassing *in vitro*, *in vivo*, and *in silico* analyses. For instance, "Kabasura Kudineer" (KSK), which contains bioactive compounds from several herbs (Table **2**), exhibits binding affinity with the SARS-CoV-2 S protein, potentially inhibiting ACE2 receptors. Similarly, "Nilavembu Kudineer" (NVK), comprising 9 herbs (Table **2**), contains the phytochemical andrographolide, which has demonstrated the capability to bind to the enzyme Main Protease (M^{pro}) [43]. Ayurvedic Rasayana encompasses phytoconstituents like ashwagandhanolide and withacoagin, which show potential docking capabilities with SARS-CoV-2 S protein. Numerous clinical trials in various phases are either ongoing or completed, investigating the use of Ayurvedic formulations. These trials indicate early recovery from COVID-19 infection (AYUSH 64/500 mg each capsules/Tid) and reduced viral load

Table 2. List of some most commonly used medicinal plants with potential therapeutic effects against COVID-19.

Regions	Medicinal Plants	
China (CHM formulas)	LQ (capsule) [39]	Forsythia fruit (*Forsythia suspensa* (Thunb.) Vahl), honeysuckle flower (*Lonicera japonica* Thunb.), fried ephedra stem (*Ephedra sinica* Stapf), dryopteris root (*Dryopteris crassirhizoma* Nakai), isatis root (*Isatis indigotica* Fort.), gypsum (*Crystalline gypsum*), patchouli (*Pogostemon cablin* (Blanco) Benth.), integripetal rhodiola herb (*Rhodiola saera* (Prain) Fu), houttuynia (*Houttuynia cordata* Thunb.), rhubarb root and rhizome (*Rheum palmatum L.*), fried apricot seed (*Prunus armeniaca* L. var. ansu Maxim.), licorice root (*Glycyrrhiza uralensis* Fisch.)
	Xuanfei Baidu (decoction) [42]	*Ephedra sinica* Stapf (Ma Huang; Stem), *Prunus armeniaca L.* (Xing Ren; Seed), *Gypsum fibrosum* (Sheng Shi Gao; inorganic substance), *Coix lacryma-jobi L.* (Yi Ren; Seed), *Atractylodes lancea* (Thunb.) DC. (Cang Zhu; Root), *Pogostemon cablin* (Blanco) Benth (Huo Xiang; Root), *Artemisia annua L.* (Qing Hao; Whole plant except root), *Reynoutria japonica* Houtt (Hu Zhang; Root), *Verbena officinalis L.* (Ma Bian Cao; Whole plant except root), *Phragmites communis* Trin (Lu Gen; Root), *Lepidium apetalum* Willd (Ting Li Zi; Seed), *Citrus reticulata* Blanco (Ju Hong; Fruit), *Glycyrrhiza uralensis* Fisch.ex DC. (Zhi Gan Cao; Root)
India (Ayurvedic formulations)	KSK [43]	*Sida acuta, Andrographis paniculata, Tinospora cordifolia, Plectranthus amboinicus, Justicia adhatoda, and Costus speciosus*
	NVK [43]	*Andrographis paniculata, Vetiveria zizanioides, Zingeber officinale, Piper nigrum, Mollugo cerviana, Santalum album, Trichosanthes cucumerina, Cyperus rotandus*
Malawi [3]	-	*Azedarachta indica* (neem)
Tanzania [51]	-	*Eucalyptus globule* (vapour), fruits of lemon and pepper, tubers of ginger, garlic, onion and carrot (mixed juice cocktail)
Indonesia [56]	-	*Zingiber officinale* (powder, tea), *Curcuma longa L.* (powder), *Curcuma xanthorriza Roxb., Camellia sinensis* (tea)
Saudi Arabia [61]	-	*Zingiber officinale, Nigella sativa* (capsule), *Allium sativum, Curcuma longa*

Note: Abbreviations are available in the main text; prepared forms of medicinal plants are mentioned according to their availability in the papers referred to in the main text.

Table 3. Nigerian medicinal plants with potential therapeutic effects against COVID-19 [35].

Antiviral	Anti-inflammatory	Antioxidant	Antipyretic	Cytoprotective
Echinacea purpurea (extraction, capsule)	*Curcuma longa*	*Allium sativum*	*Enantia chlorantha*	*Allium cepa*
Boerhavia diffusa	*Zingiber officinale* (powder)	*Zingiber officinale*	*Khaya grandifoliola*	*Artemisia annua*
Phyllanthus spp. (aqueous extract)	*Moringa oliefera*	*Crocus sativus*	*Azadirachta indica*	*Azadirachta indica L.*
Andrographis paniculata (ethanol extract)	*Asparagus africanus*	*Dodonaea viscose*	*Morinda lucida*	*Camellia sinensis*
Borreria verticillata	*Cassia occidentalis*	*Datura fastuosa*	-	*Citrus aurantium*

Note: Prepared forms of medicinal plants are mentioned according to their availability in the papers referred to in the main text.

(Kabasura Kudineer/60 ml twice a day/14 days). Additionally, combining Ayurvedic supplements with conventional treatments may expedite the recovery period (AYUSH−64/2 tablets (500 mg each)/Tid). However, the exact mechanisms contributing to the observed reduction in recovery time in these trials are not yet fully understood [44].

4.2.3. Therapeutic Effects of African Medicinal Plants for COVID-19

According to the WHO Traditional Medicine Strategy (2014-2023) report released on December 14, 2022, the Regional Expert Advisory Committee on Traditional Medicine for COVID-19 in the Africa Region was established in 2020 [45]. The effectiveness of various Nigerian medicinal plants, long used in folk medicine for managing diverse diseases, has been well-established. The African Center of Excellence for Drug Research, Herbal Medicine Development, and Regulatory Science (ACEDHARS) aims to create a platform for extensive investigations into the safety and efficacy of herbal medicines, particularly sourced from Nigeria and across Africa, to develop anti-COVID-19 drugs using natural products [12]. Several Nigerian medicinal plants exhibiting therapeutic potential, which could potentially serve as an effective therapy for COVID-19, have been highlighted by Oladele *et al.* (Table **3**) [35]. The results of a clinical trial comprising 40 participants have revealed that *Echinacea purpurea* (400 mg/per day/28 days) down-regulates the expression of TMPRSS2, one of the determinant factors of susceptibility of target organs to SARS-CoV-2 infection. It is likely polysaccharides play a key role in the reduction of pro-inflammatory cytokines such as IL-1β, IL-6 and TNF, thereby inhibiting SARS-CoV-2 entering the target cell [46, 47].

In Malawi, *Azedarachta indica* (neem) stands out as a medicinal plant demonstrating effectiveness in alleviating COVID-19-related symptoms [3]. Eze and colleagues propose that the acetone-water extract of neem leaf could serve as a potent therapeutic remedy for COVID-19 by impeding the access of SARS-CoV-2 to vascular endothelial cells, a process associated with the pathophysiology of viral infection [48]. However, there are some points of concern regarding Indica. Variability in the preparation of plant extractions (alcoholic *vs* aqueous, for example), as well as discrepancies in concentration, lead to ambivalence in the safety and efficacy of the plant. The degeneration of hepatocytes in mice has been evidenced by Lisanti *et al*. after oral administration of aqueous seeds extract of neem (0.25 and 0.50 mg/kg body weight/36 days) [49]. The determination of the lethal dose (LD_{50}) of certain plant extracts provides an opportunity to discover safe biological products. While 31.95 g/kg has been defined as LD_{50} for neem oil, *in vivo* toxicity investigations explored that neem oil at doses up to 1600 mg/kg/per day, does not cause histopathological alterations of target organs including testicles, liver and kidneys [50]. These findings attest to the importance of administering extracts from medicinal plants under an expert's supervision.

Traditional practitioners in Tanzania have recommended the use of extracts derived from *Eucalyptus globulus* leaves (administered through inhalation of hot vapours), along with a combination of lemon and pepper fruits, ginger, garlic, onion, and carrot tubers in the form of a mixed juice cocktail to combat COVID-19. The presence of various secondary metabolites such as flavonoids, terpenes, tannins, saponins, glycosides, alkaloids, steroids, and fatty acids in these natural sources has been investigated by researchers. The antiviral properties of tannins and flavonoids, notably in inhibiting viral DNA and RNA replication as well as impeding viral RNA synthesis, have been described [51, 52]. Notably, the essential oils extracted from Eucalyptus (rich in fatty acids and terpenes) have exhibited a strong affinity to the SARS-CoV-2 enzyme M^{pro}, crucial for viral maturation [53]. Furthermore, a recent computational study focused on selected alkaloids possessing protease-inhibitory properties has been conducted to assess the characteristics of these bioactive compounds as potential inhibitors of SARS-CoV-2 [54]. The results of a meta-analysis of six randomised controlled trials comprising 1,857 participants revealed that pure Eucalyptus extract (cineole 200 mg/3 times/daily) and mixed preparations of Eucalyptus oil (12 mcg/4-5 times/daily; 300 mg/3-4 times/daily) significantly improved cough symptoms (n=1,061, RR:1.45, 95% CI 1.26-1.67, p-value <0.001) and cough frequency compared to placebo (n=655, WMD: 0.44, 95% CI 0.28-0.60, p-value <0.001). Heartburn, nausea, diarrhoea and stomach ache have been reported as mild-to-moderate adverse events [55]. The effective application of Eucalyptus oil to relieve cough severity and frequency suggests its potential as a treatment option for COVID-19 symptoms.

4.2.4. Therapeutic Effects of Indonesian Medicinal Plants for COVID-19

Red ginger (*Zingiber officinale*), turmeric (*Curcuma longa L.*) and Javanese turmeric (*Curcuma xanthorriza* Roxb.), belonging to the Zingiberaceae family, along with green tea (*Camellia sinensis*) from Theaceae family, are identified by Purwitasari and colleagues as crucial Indonesian medicinal plants with potential as a treatment for COVID-19 [56]. *Z. officinale* is recognised as a constituent of various combined herbal extracts, and its widespread use can be attributed to its bioactive phytochemicals. Particularly, 6-gingerol, a pungent compound present in ginger, exhibits the ability to inhibit SARS-CoV-2 replication by targeting the virus-related papain-like protease (PLpro). Additionally, docking analysis has revealed that 4-gingerol possesses the lowest binding energy against M^{pro}, suggesting its potential candidacy in designing antiviral agents for COVID-19 treatment [57]. Furthermore, evidence from mouse models of respiratory viral infection and experimental autoimmune encephalomyelitis (EAE) mice indicates that ginger extract down-regulates oxidative stress and modulates Treg cell-mediated responses. These mechanisms are significant in the pathogenesis of COVID-19 [58]. Catechins, the primary biologically active polyphenolic compounds found in *C. sinensis* leaves, demonstrate antioxidant, anti-inflammatory, and antiviral activities. Docking results have indicated that catechins can inhibit the 3-chymotrypsin-like cysteine protease (3CLpro), a protein essential in processing viral polyproteins post-infection, suggesting their potential role as inhibitors in combating COVID-19 [59, 60].

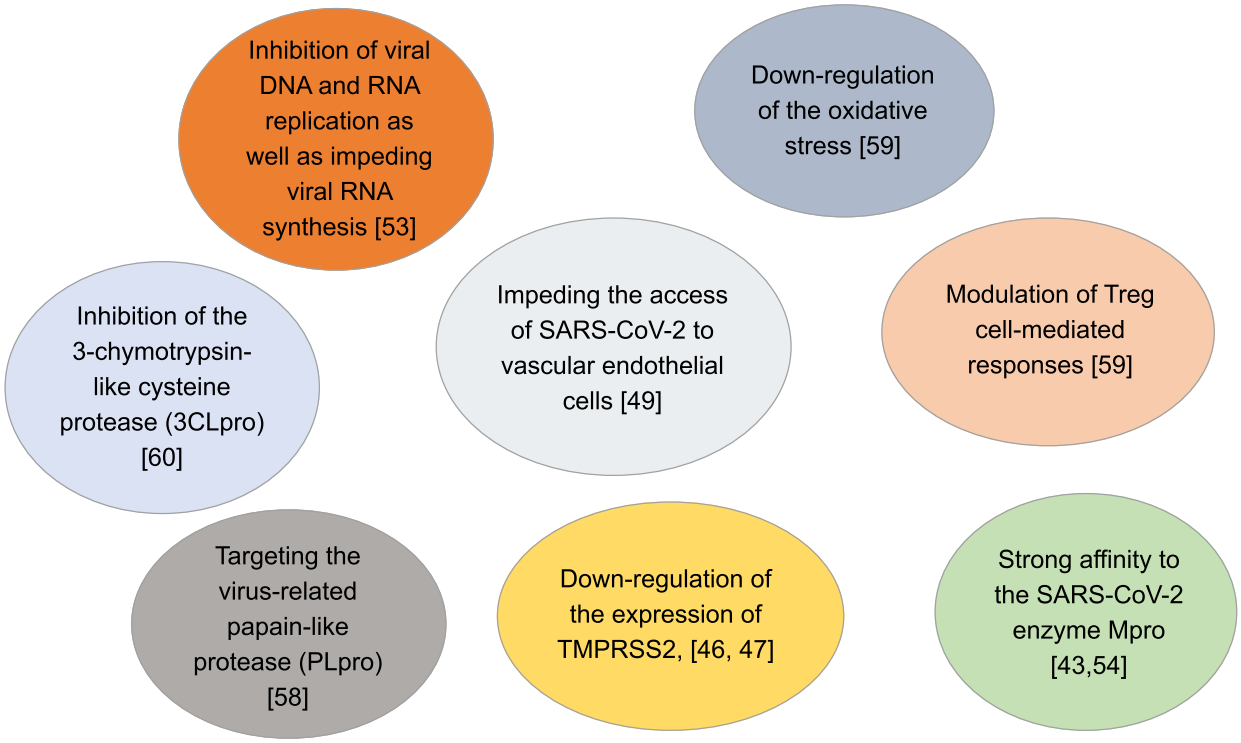

Fig. (3). Putative therapeutic effects of various types of medicinal plants on COVID-19.

4.2.5. Therapeutic Effects of Medicinal Plants in Saudi Arabia for COVID-19

Almuqbil and colleagues [61] highlighted a significant increase in the demand for medicinal plants across various regions in Saudi Arabia during the pandemic, specifically for alleviating symptoms akin to COVID-19. Among these plants, *Z. officinale* emerged as the most commonly utilised, followed by black seeds (*Nigella sativa*), *A. sativum*, and *C. longa*, respectively. *Z. officinale* was predominantly chosen for relieving coughs and sore throats associated with COVID-19, while *A. sativum* was used to address coughs and fatigue. *N. sativa* was also employed to combat fatigue during this period. The antiviral effects of *N. sativa* have been demonstrated through various *in vivo* studies. A single-armed, self-controlled pilot study on 30 hepatitis C virus (HCV) patients evaluated liver function after receiving *N. sativa* seed oil

capsules (450 mg/3 times a day/for 3 months). Examining HCV RNA levels (PCR) revealed a significant decrease in viral load following 3 months (from 380808.7± 610937 to 147028.2 ± 475225.6, P = 0.001). Furthermore, clinical evidence has shown that *N. sativa* seed hydro-ethanolic extracts ameliorate respiratory symptoms and pulmonary functions (15 mg/kg/per day/for a 3-month and 50, 100 mg/kg/per day/p.o. respectively) [62]. The toxicity of *N. sativa* extracts has been reviewed by Mashayekhi-Sardoo and colleagues. LD_{50} for administered *N. sativa* essential oil has been reported as 28.8 ml/kg to 3,371 mg/kg in mice and is generally safe in humans [63]. However, more thorough and updated trials are necessary to comprehensively assess the safety of the plant extract.

The therapeutic effects of various types of medicinal plants on COVID-19 are summarised in Fig. (**3**).

5. PERSPECTIVE FOR USING MEDICINAL PLANTS IN MANAGING COVID-19

The WHO's 2014-2023 Strategy on Traditional Medicine strives to enhance and facilitate the integration of Traditional and Complementary Medicine (T&CM) into the national healthcare systems of its member states. In recent times, many member states have taken steps to regulate herbal medicines, often produced in one country and sold in another, in order to ensure their safety and quality standards [64]. While TCM originated in China, its global appeal has steadily grown alongside its availability. Thus, the establishment of appropriate standardised regulatory systems for registering these products has become essential. Some countries have proposed streamlining the registration process for products with a long history of usage [65]. For example, in Poland, despite there being growing public interest in alternative medicine and a longstanding interest in TCM, the absence of a regulatory framework specifically for Chinese herbs remains a concern [66]. Designing disease prevention strategies across countries, integrating traditional medicine into conventional treatments, fostering public awareness of locally cultivated herbal remedies, and regulating and standardising medicinal plants are all potentially effective approaches for future COVID-19 treatments. However, careful consideration of possible challenges arising from toxicity, drug-herb interactions, and allergic reactions necessitates further investigation across the board.

6. STUDY LIMITATIONS

This study has several potential limitations that warrant consideration. Despite the multiregional scope of the review, increasing the number of studies specifically focusing on regions within a particular geographical area may increase its value. Furthermore, a comparison of the most commonly used medicinal plants across the countries addressed in this review was not conducted. Despite the abundance of herbal therapeutic formulations in TCM and Ayurvedic medicine, only a select few were discussed in this review. To better understand the prevalence of herbal preparation use beyond their regions of origin, more comprehensive studies are necessary. Moreover, the combination of herbal medicines with other chemicals may lead to synergistic effects which have not been addressed. Detailed observations and trials are required to discover potential interactions of individual medicinal plants with commonly employed conventional therapies. Molecular docking is a rapid and cost-effective tool in the drug discovery process and is used for developing potential drug candidates. Numerous studies have been designed to identify beneficial conventional nutraceuticals for use against SARS-CoV-2. However, several challenges remain in the accuracy of different steps of molecular docking [67, 68]. Besides, *in silico* docking analyses are designed without consideration of the pharmacokinetics of phytochemicals, which may affect the certainty of the results [69].

Wet lab experiments must be performed to corroborate the biological activity predicted with docking. It is obvious that the health benefits of phytochemicals are dose/ concentration-dependent. However, Chinese versions of original papers restrict access to some TCM formulas, their therapeutic concentrations, and modes of preparation of medicinal plants. Furthermore, some of the studies included in this review have reported the prevalence of usage and categorisation of different medicinal plants without specifying therapeutic dosage, duration of treatment, and form of administration. Therefore, designing higher-quality studies is recommended, especially with a view to obtaining accurate data on therapeutic concentrations of medicinal plants, treatment protocols, and information on their preparation and administration.

CONCLUSION

The exploration of medicinal plants in addressing COVID-19 has captured global interest among phytotherapy researchers. These plants have a longstanding history of managing various respiratory infections and are prevalent across different countries and regions, occupying a significant role in community healthcare. TCM, Ayurveda, and African traditional medicine stand as historical pioneers in the realm of medicinal botanicals. Progressing scientific research within this field and developing patented, plant-based medications may be proactive strategies for managing not only the ongoing pandemic but also in preparing for potential future outbreaks.

LIST OF ABBREVIATIONS

RTIs	=	Respiratory Tract Infections
SARS-CoV-2	=	Severe Acute Respiratory Syndrome Coronavirus 2
WHO	=	World Health Organization
PHEIC	=	Public Health Emergency of International Concern
WIE	=	Water Ingredient Extract
WBC	=	White Blood Cells
NK	=	Natural Killer
ACE2	=	Angiotensin-converting Enzyme 2

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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