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EVIDENCE OF PAKISTANI TRADITIONAL MEDICINAL PLANTS IN SARS-CoV-2 AS ADJUNCTIVE SYMPTOMATIC THERAPY: PRECLINICAL AND CLINICAL STUDIES

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Abstract

Since the outbreak of the coronavirus problem in 2019, millions of fatalities have occurred worldwide. Till todate, absenteeism of SARS-CoV-2 specific medication is severe reality. Urge to overcome COVID-19 epidemic need an identification of all possible therapeutic targets. This can be attainable by turning cornerstone towards traditional medicinal plants (TMPs), already used for management of other fetal diseases. Pakistani TMPs/ bioactive compounds evaluated for their efficacy assessment/safety profile against COVID-19 pathogenesis, manifestation and complications via preclinical and clinical data from authentic sources. Executed investigations on effectiveness of TMPs are classified as antiviral, anti-inflammatory/ Immune-dilatory in COVID -19 patients and inhibitor of structural, nonstructural proteins (RdRp and the viral proteases such as papain-like protease /PLpro and main protease /Mpro) and human inflammatory proteins in molecular docking analysis. Docking scores exhibited their inhibitory potential against entry and replication of SARS-CoV-2. Molecular Mechanics energy combined with Generalized Born and Surface Area continuation salvation method (MM/GBSA) confirmed highest receptor-ligand (TMPs/Bioactive compounds and protein/enzymes of coronavirus) affinity with high stability profile. Accomplishment of successful clinical trials on TPMs, proved their competence to interfere with COVID-19 manifestations. This article provides up-to-date effectiveness/safety profile particulars TMPs/Bioactive compounds, as adjunctive treatment and supportive therapy in SARS-CoV-2 due enough level of evidence, via preclinical and clinical data.

Key words: Bioactive compounds, COVID-19 epidemic, Adjunctive treatment, Pathogenesis, clinical trials, Safety profile of TMPs, Molecular docking.

Introduction

SARS-CoV-2 originated from novel coronavirus in seafood market of Wuhan. SARS-CoV-2 pandemic caused hundreds thousands mortalities globally. To cope up with sheer infected persons necessitates utilization all possible way to generate anti-COVID therapy (Arshad, 2022; Alam, *et al*., 2021; Hosoki *et al*., 2020). Pathogenesis starts with viral attachment to Angiotensin converting enzyme 2 (ACE-2) receptor only located on respiratory epithelia with ligand of SARS-CoV-2 spike proteins (Pandamooz *et al*., 2022). Attachment may result in sequel of invasion, pneumonia and fluid buildup on alveoli, RNAemia, and acute cardiac & renal injury (Sparke *et al*., 2022; Mirzaie *et al*., 2020). Pro-inflammatory cytokines and chemokines like TNF-α, interleukin (IL)-2, IL-6, IL-7, IL-8, IL-10,) and macrophage inflammatory protein 1-alpha (MIP1-alpha) condition named "cytokine storm" often noticed in serum of critically ill patients (Kim *et al*., 2021; Zhang *et al*., 2021), main cause of demise (Diao *et al*., 2020). In adults, the most common symptoms appear in five days, which include cough, fever, and fatigue. Additional manifestations include headache, hemoptysis, and dyspnea (Xu *et al*., 2020; Kloc *et al*., 2020; Li & Xia, 2020). Mostly signs are analogous in children, whereas rhinorrhea, GIT complications are compare to adults (Grant *et al*., 2020; Bornstein *et al*., 2020). However aged patients and cases with multiple comorbidities (cerebrovascular, cardiovascular, endocrine disease, respiratory, immunodeficiency and digestive) experience severest form of disease (Idrees *et al*., 2021; Gautret *et al*., 2020). TMPs already been applied to treat different viral infections and prescribed as supportive therapy (Younis *et al*., 2018; Umar *et al*., 2021; Alhazmi *et al*., 2021; Anand *et al*., 2021). Literature search revealed, TMPs significantly treat infectious diseases, because potent phytochemicals own antiviral, anti-inflammatory and immune dilatory properties (Asif *et al*., 2020; Magzoub *et al*., 2020). Nevertheless, effectiveness and safety profile of these TMPs in other viral infections may be different from SARS-CoV-2. Most of these TMPs being inspected in lot of preclinical and clinical studies at various stages for COVID-19 (Gowrishankar *et al*., 2021). These studies carried out to find the efficacy /safety profile to scrutinized bioactive components of TMPs for therapeutic purposes. This research is planned to gather potent TMPs with bioactive components, which have examined pre clinically or clinically in both adjunctive treatment and supportive anti-COVID therapy for this new coronavirus infection.

This review presents two sections on preclinical and clinical efficacy assessment of TMPs in management of SARS-CoV-2. First section includes molecular docking analysis of effective TMPs against SARS-CoV-2 pathogenesis description via inhibiting structural, nonstructural proteins of SARS-CoV-2 (3CLpro, ACE-2, spike glycoprotein and RdRp) and human inflammatory proteins. In second section, all available clinical studies of potent TMPs (possess antiviral and Immunomodulatory/ Anti-inflammatory) against manifestations and in control of SARS-CoV-2.

Article search strategy and methodology: Literature search was conducted to summarize the finding regarding SARS-CoV-2 in-silico/ molecular docking analysis of traditional medicinal plants against pathogenesis and completed and/or recruiting clinical trials of traditional medicinal plants as therapeutic agents through PubMed, Web of Science, Google Scholar and Scopus, Science Direct, Wiley Online Library, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov database. The prime source of search

for clinical trials was the ClinicalTrials.gov website (https://www.clinicaltrials.gov/) because of its authenticity. Following keywords "COVID-19," "SARS-CoV-2," "PLpro," "RdRp," "spike protein," "ACE-2," "M^{pro}/$3CL_{pro}$" and "human inflammatory proteins" "molecular docking analysis," "bioactive compounds," "traditional medicinal plants," "herbal plants," "anti- COVID-19," and "clinical trials". considered as the critical part of search for this review. All completed papers on COVID-19 pathogenesis and/or recruiting clinical trials and/or molecular docking studies highest receptor-ligand were included in the final review. Limitations of the subject area are medicine, pharmacology, safety profile, therapeutics. Initially, 345 papers including clinical trials were identified till December 2021. After excluding paper and abstracts related to Chinese traditional medicinal plants, traditional medicinal plants used in treatments other than SARS-CoV-2, pharmaceutical as not related to scope of review. Finally, 80 unique articles and clinical trials were identified that met the criteria and purpose of this review (Fig. 1). Fifty-seven traditional medicinal plants or their bioactive components active against SARS-CoV-2 were included in this review.

In start of review, crucial points in the pathogenesis of SARS-CoV-2 used to elucidate the mechanism that might play significant role in control & prevention of manifestations and adjunctive treatment. After that, in-silico/ Molecular docking analysis of forty-two traditional medicinal plants or their potent bioactive components exhibited positive comparable results (as antiviral component) with antiviral chemical drugs (significant docking score against structural, nonstructural proteins; $3CL_{pro}$, ACE-2, spike glycoprotein, PLpro and RdRp of SARS-CoV-2 and human inflammatory proteins) and *in vivo* studies were cited. In last, completed and/or recruiting clinical trials or/and retrospective/case studies of TMPs or their bioactive components (Having antiviral and immune-dilatory activity with consideration of SARS-CoV-2 pathogenesis mode in human) were presented.

Molecular docking studies of potent TMPS /bioactive components against SARS-CoV-2 pathogenesis: Most of the research revealed two crucial targets in SARS-CoV-2 pathogenesis as First, blocking the spike glycoprotein of SARS-CoV-2 from entry in host alveoli cell via a specific receptor Angiotension Converting Enzymes (ACE-2,) (Shawky *et al*., 2020; Ahmed *et al*., 2020). Second, inhibition of non-structural proteins needed for replication of SARS-CoV-2 including main protease (3CLpro), papain like protein (PLPro) and RNA directed RNA polymerase (RdRp) inhibition (Shree *et al*., 2020).

The SARS-CoV-2 spike (S) protein is largest protein among four structural proteins named as nucleocapsid, membrane envelope proteins (M, E and N proteins). The SARS-CoV-2 S glycoprotein has two subunits; S1 (receptor-binding domain) that involves with host cell receptor angiotensin-converting enzyme-2 (ACE-2) and S2 mediates fusion of virus and host cell at membranes level (Natesh *et al*., 2021; Mondal *et al*., 2020). Activation of S protein is dependent on conformational changes and proteolytic cleavage before fusion with ACE-2 receptor. In short, S protein performs as guiding manual for virus-host cell attachment. In primary stage of pathogenesis, coronavirus enters inside host cell and replicate. In initiation phase, virus pathogenesis could be obstacle by virus entry blockers (Jalali *et al*., 2021; Dutta *et al*., 2021). Angiotensin Converting Enzymes-2 (ACE-2) receptor is only expressed in alveoli cell of lungs and small intestine serve as main entrance point for COVID -19 in host cells (Djomkam *et al*., 2020). Hence, vital body organs could be under attack because of SARS-CoV-2. Virus needs proteolytic cleavages to get active conformation for generating functional replication complexes to facilitate viral infection. Finally, SARS-CoV-2 encodes main protease/ Mpro /3CLpro, PLpro and RdRp.

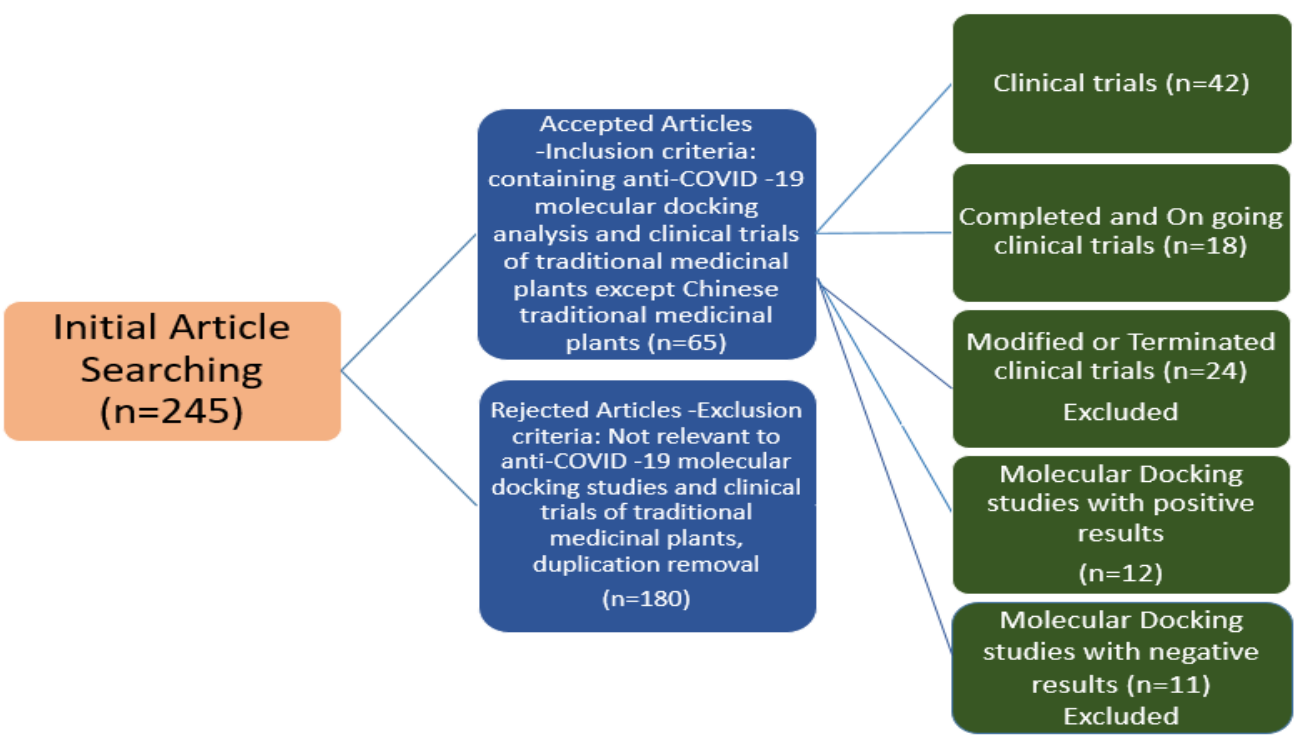

Fig. 1. Diagrammatic representation of article search stratergy.

In SARS-CoV-2, Papain-Like Protease (PLpro) and 3-Chymotrypsin-Like Protease (3CLpro), generate 16 nonstructural proteins (Mody *et al*., 2020). Both PLpro and 3CLpro serves as promising antiviral targets (Li & Kang, 2020). Viral RNA-dependent RNA polymerase (RdRp) plays crucial role in synthesis of 5′-3′ polynucleotides template during replication of SARS-CoV-2. Moreover, RdRp is indispensable for initiation of RNA replication in the host cell (Gil *et al*., 2020; Henderson *et al*., 2020). RdRp is well-known target for halation of SARS-CoV-2 - RNA replication and viral growth. If virus is bypassed first check post and enter into host cell, then second frequent blocking point is inhibition of critical non-structural proteins (RdRp and the viral proteases such as papain-like protease /PL^{pro} and main protease /M^{pro}) in SARS-CoV-2, which could serve as valuable antiviral targets (Rivero-Segura & Gomez-Verjan, 2021; Pillay, 2020).

For this purpose, bioactive components of traditional medicinal plants, targeted against pathogenesis could prevent COVID-19 infection, announced as antiviral (inhibitory) agents. Hence, In-silico/ Molecular docking/ molecular modeling studies of important traditional plants or bioactive components striking the spike glycoproteins, ACE-2, main protease/ Mpro/3CLpro and PLpro and RdRp in inhibition of SARS-CoV-2 entry and replication within host cells identified (Dermawan *et al*., 2021; Henderson *et al*., 2020). Molecular docking investigations, based on positive results of 42 traditional medicinal plants or bioactive components presented in Tables 1 & 2.

Information coated in Table 1 confirms that docking score of selected traditional medicinal plants and their bioactive components have effectiveness to interfere with proteolytic activity of COVID-19 3CLpro, PLpro and RdRp and might have therapeutic potential against current coronavirus pandemic. However, validation of these studies is required in animals and SARS-CoV-2 patients. Recorded ligand receptor binding efficacy of *Nigella sativa* L. for its bioactive component "nigillidine" in docking experiment with structural protein N (nucleocapsid), Mpro (Main protease nonstructural protein), Nsp2 (nonstructural RNA binding protein) and human inflammatory receptor protein -0.3, -0.28, -0.28, -0.29 respectively. However, ligand "nigillidine" interact with nonstructural RNA binding protein Nsp2 with a maximum docking score of -6.6 (Maiti *et al*., 2020). "Withanoside II" (PubChem CID-101168811) active component of *Withania somnifera* (L.) *Dunal* possessed maximum binding free energy, which is -11.30 Kcal/mole compared to control N3. During complex formation with Mpro SARS-CoV-2 "Withanoside-II" form 4 H-bonds with His-41, Thr-26, Ser 46 & Ans-142 and four hydrophobic interactions with Cys-145, met-49, Met-165 & Pro-168 (Prasanth *et al*., 2020).

However, free energy calculations (100 conformations between 60-100 ns timeframe of Molecular Dynamics production run) of Molecular Mechanics energy combined with Generalized Born and Surface Area continuation salvation method (MM/GBSA) widely used to find ligand binding affinities. Results revealed that "Withanoside-V" (with Mpro enzyme) had highest receptor-ligand affinity with high stability profile (Tripathi *et al*., 2020). MM-PBSA (Molecular Mechanics-Poisson -Boltzmann Surface Area) method provides the accurate binding behaviors of "Anisotine" with spike protein & Mpro (Bioactive component of *Justicia Adhatoda* L.) and "Amarogentin" potent bioactive component of *Ocimum sanctum* L. with RdRp (protein- ligand complex) forming 4, 4 and 13 hydrogen bonds respectively (Kar *et al*., 2022). Although "Anisotine" from *Justicia Adhatoda* L. showed comparable inhibition potency in docking experiment with strongest anti-COVID adjunctive chemical drugs lopinavir and Darunavir. Anisotine inhibits proteolytic activity of SARS-CoV-2 by forming two H-bonds at Mpro active site. RMSF Analysis revealed less conformation fluctuations and high stability profiler of Mpro and "Anisotine" (Nair *et al*., 2020; Ghosh *et al*., 2021). During *in vivo* experiments in rats, "Tenufolin" and "Pavetannin" showed LD_{50} value 3.014 & 2.105 mol/kg and both revealed as nontoxic and carcinogenic. Interaction of "Tenufolin" and "Pavetannin" bioactive components of *Cinnamomum verum* J. Presl (cinnamon) with spike protein, Mpro and human inflammatory receptor protein exhibited that "Pavetannin" could sever as crucial target for new drug discovery because of its high safety standards (Nair *et al*., 2020; Prasanth *et al*., 2020).

Silybum marianum (L.) *Gaertn, Mangifera indica* (L.), *Moringa oleifera* Lam, *Azadirachta indica* A.Juss, *Panx Ginseng, Glycyrrhiza glabra* L., *Eucalyptus globulus Labill. (Eucalyptus), Strobilanthes Cusia, Isatis indigotica, Berberis aristata* DC., *Ficus Microcarpa, Tinospora cordifolia (*Willd*.) Miers* and *Ocimum sanctum* L. possess numerous bioactive compounds having capability to interact with ACE-2, Spike glycoproteins, RdRp, Mpro, main protease Nsp5 and Plpro in docking simulations (Alhazm *et al*., 2021; Ahmed *et al*., 2020; Jalali *et al*., 2021; Garg *et al*., 2020; Khanna *et al*., 2020).

Clinical studies of potent TMPs/bioactive components as therapeutic agents for sign and symptoms of SARS-CoV-2: SARS-CoV-2 infection leads to numerous manifestations and signs in COVID -19 positive persons such as cough, shortness of breath, pyrexia, headache, hemoptysis, and tiredness (Arshad *et al*., 2021; Xu *et al*., 2020). Pyrexia is the usual manifestations in COVID-19 patients (Chen *et al*., 2020). Body's homeostat is abruptly changed due to diseased condition of the person. Thermoregulator (hyppthalmus) raised the set body temperature under influence of pro-inflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor (TNF) and interleukin-6 (IL-6) released in patients. Although, Pyrexia looks for healing booster through upregulating leukocytes 'activity, but the whole process persuades excessive formation of pro-inflammatory proteins and antipyretic cytokines interleukin 10 (IL-10) (Aronoff & Neilson, 2001). Subsequently, all these events lead towards triggering of exacerbated condition named "cytokine storm" (elevated levels of tumor necrosis factor alpha, interleukin-6 &10), in exacerbated COVID-19 patients by high blood levels of TNF-α, IL-6, and IL-10, instead of healing (Mehta *et al*., 2020). As described earlier, Pyrexia control and immuno-modulators concentration perform a crucial role in treatment of SARS-CoV-2 Noted as various antipyretics drugs could lessen body temperature by indirect inhibitory attack on

cyclooxygenase, however careful selection of cytokines modulation could improve effectiveness in treatment of COVID-19. Severe dry cough is additional complication in COVID-19 patients triggered by inflammatory secretion in the airways (Tripathi *et al*., 2020). Despite of the fact that, cough is a chief defensive mechanism of lungs, excessive cough can lead to harmful complications such as headache, pulmonary emphysema, trauma of upper respiratory tract, cardiac arrhythmia, in short patient's is at risk (Narkhede *et al*., 2020; Gallelli *et al*., 2020).

Bronchitis and irritation in airways due to heavy cough suffered by mostly COVID-19 patients. At that point, cough suppressant drugs prescription, with immune dilatory effects, could serve as relief. So traditional medicinal plants with their antiviral, immuno-dilatory potential could be new target for drug discovery. So up to date conducted therapeutic anti-COVID-19 clinical trials of different TMPs and their bioactive compounds are manifested in Table 3.

Effectiveness of Honey and *Nigella sativa* L. (Black seed) in management of COVID-19 infection, was evaluated (Phase 3 study) in 313 COVID-19 patients (registered clinical trial with no NCT04347382, HNS-COVID-PK) admitted at Medical Institute (Federal Post-Graduate), Services Institute (Medical Sciences) and their associated hospitals Shaikh Zayed and Services Hospital Lahore, Pakistan. COVID-19 participant's selection was done according to the following inclusion criteria (156 control and 157 on HNS) both male and female, age above 18 years, 210 with moderate (107 in HNS & 103 control group) and 103 with severe infection (50 in HNS & 53 in placebo group) presented in Table 3. Powdered *Nigella Sativa* L. (black seed) 80 mg/Kg/day and natural honey 1gm/kg/day administered orally 2 to 3times to patients, till 13 days of investigation and 1-month mortality, to suppress harshness of disease signs along with length of hospital stay and full shedding of COVID-19 nucleic acid from patient's body. (Ashraf *et al*., 2022).

Iranian Registry of Clinical trial (IRCT20200506047323N2) evaluated anti-inflammatory efficacy (as natural medicine of *Glycyrrhiza glabra* L. (Licorice) root extract, on clinical manifestations and laboratory signs of COVID in infected persons admitted at Shahid Mohammadi Hospital, Iran. The approved treatment protocol for experimental COVID-19 group in addition with *Glycyrrhiza glabra* L. formulation (D-Reglis ®, Iran) of concentration 760 milligram thrice a day along with recommended continuation of week, while the standard treatment procedures for control group in accordance with protocol designed by Iranian governing body of health with same duration. Study results are not yet shared (Safa *et al*., 2020a).

Iranian Registry of Clinical Trials (IRCT) with number, "IRCT20200506047323N1" a clinical trial registered to find out the effects of *Zingiber officinale* Roscoe (Ginger) on clinical symptoms and para-clinical characteristics of COVID-19 infection in positive patients admitted at Shahid Mohammadi Hospital, Bandar Abbas, Iran. *Zingiber officinale* Roscoe pills (Vomigone ®, Iran) of 1 g thrice a day for a period of week in addition to standard treatment procedures for COVID-19. Results of this study not published yet (Safa *et al*., 2020 b).

Clinical Trial Registry of India registered a clinical trial with no. CTRI/2020/07/026570 to evaluate safety profile and effectiveness of medicinal herb extracts "ayurved" to replenish lungs health and innate immunity in COVID-19 patients attending therapy at Memorial Hospital (Yashwantrao Chavan), Nehrunagar, Pimpri, Pune, India. Efficacy of 'ayurved' named Investigational Product comprised of [IP1] *Zingiber officinale* Roscoe, *Embelia ribes* Burm.f., *Glycyrrhiza glabra* L., Shankhabhasma abd Jasath Bhasma. and Investigational Product [IP2] composed of *Terminalia chebula* Retz. (chebulic myrobalan), *Tinospora cordifolia* (Willd.) *Miers* (guduchi), *Asparagus racemosus* Willd. (Satamuli), *Emblica officinalis* Gaertn. (gooseberry or amla), *Piper longum* L. Calcined Zinc, Shankhabhasma) checked in early recovery and decline in viral load, safety of herbal extracts in COVID-19 patients. 39 patients in experimental arm vs 33 in control arm, both male and female (p=0.336) age above 18 years, with slight to modest COVID-19 infection from last 10 days. 52 patients (21 from placebo and 31 from IP) had qRT-PCR before start of trial and at 4th day. For experimental Arm prescribed to take one capsule twice daily (both IP 1 & 2) with dose concentration of 400 & 450 mg for a month (Rangnekar *et al*., 2020; Patankar *et al*., 2022).

A clinical trial no. NCT04401202 (phase 2 study) designed to evaluate effectiveness of *Nigella sativa* L. (NS) oil administration in COVID-19 patients hospitalized at King Abdulaziz University Hospital, Jeddah, Saudi Arabia. For Intervention Arm, standard treatment procedures (antipyretic, antitussive) plus *Nigella sativa* L. oil (MARNYS® Cuminmar) 0.5 g soft gel capsule orally, 2 times after twelve hours daily for one and half week. While placebo group on standard treatment procedures. Main finding of the clinical trial includes proportion of recovered patients (3 days of zero symptoms) within two weeks after randomization. However, this trial is not completed yet (Koshak *et al*., 2020).

A clinical trial no. NCT04480398 designed to evaluate efficacy and Safety of Guduchi Ghan Vati for COVID-19 asymptomatic patients registered by Aarogyam UK Guduchi Ghan Vati an ayurvedic preparation (aqueous of extract of *Tinospora Cordifolia*) was given orally to COVID patients in total dose of 1000mg daily equally divided in two doses (500 mg in morning and 500 mg in evening) for 2-weeks Trial has completed its recruitment status and will be executed at NMP Medical Research Institute & Padmanabhama & Ayurveda Hospital and Research Centre of Jaipur, Rajasthan, India in collaboration with Aarogyam Leicester, United Kingdom (NCT04480398, 2020).

A clinical trial no. NCT04542876 designed to evaluate efficacy and safety of Guduchi Ghan Vati in the management of asymptomatic COVID-19 infection. Guduchi Ghana is a distinctive ayuvedic preparation of *Tinospora cordifolia* stem liquid extracts registered by Aarogyam UK in collaboration with Radhakrishnan Rajasthan Ayurved University. Recruitment phase of the trial has been completed. Prescribed amount of Guduchi Ghan Vati was 2000 mg, twice daily for 2 weeks through oral administration. (NCT04542876, 2020).

Table 1. Binding energies of different TMPs /bioactive components against structural, nonstructural proteins of SARC-COV2 and human inflammatory proteins via docking analysis.

Plant	Bioactive compound	Mechanism/Receptor ligand complex	Binding-energy (kcal/mol)	MM-GBSA	MM/PBSA	Ligand-efficiency	Reference
	Nimbolide	Nimbolide- Mpro	-7.6				Umar *et al*., 2021
	Nimolicinol c7	Nimolicinol c7- Mpro	-10.09		-31.47		Parida *et al*., 2020
Azadirachta indica A.Juss	Nimbolide	Nimbolide- PLpro.	-7.1				Baildya *et al*., 2021
	Desacetylgedunin	Desacetylgedunin- PLpro.	-7.3				
	Margocin	Margocin- PLpro.	-6.8				
	Gedunin	Gedunin -Mpro	-9.51	− 0.27			
	Epoxyazadiradione	Epoxyazadiradione-Mpro	-8.74	-0.25			Garg *et al*., 2020
	Nimbin	Nimbin-Mpro	8.66	-0.22			
A. indica, A.Juss *M. indica* and *M. oleifera* Lam	Quercetin	Quercetin-Mpro	-7.5				Umar *et al*., 2021
Berberis aristata DC	Berberine	Berberine - Mpro	-8.1				Narkhede *et al*.,2020
Cinnamomum verum J.Presl (Cinnamon)	Tenuifolin (Ten)	Mpro of SARS-CoV-2-Tenuifolin (Ten)	-8.8		-29.62 ± 3.97		Prasanth *et al*.,2020
		Spike Protein-Tenuifolin	-8.7		Not stable		
	Pavetannin C1(PAV)	Mpro-Pavetannin C1(PAV)	-7.3		Not stable		
		Spike Protein-Pavetannin-C1	-11.1		-37.97 ± 7.26		
Eucalyptus globulus Labill. (*eucalyptus)*	Bicylogermecrene,	Bicylogermecrene- Mpro	-6.5				
Ficus microcarpa	Quercetin 3,7-O-a-L-dirhamnoside	Quercetin 3,7-O-a-L-dirhamnoside- Mpro	-7.83				Narkhede *et al*.,2020
	Rutin	Rutin- Mpro	-7.42				
Glycyrrhiza glabra L.	Glycyrrhizin	Glycyrrhizin - Mpro	-8.1				
Justicia adhatoda L.	Anisotine	Anisotine- RBD- spike protein,	-7.8		-39.39±1.29		Kar *et al*., 2022
		Anisotine-SARS-CoV-2Mpro	-8.4		-42.44±1.27		
		Anisotine-- Mpro	-7.9	-42.23 ±			
M. indica A.Juss	Mangiferin	Mangiferin- Mpro	-8.4				
M. indica A.Juss and *Moringa oleifera* Lam	Ellagic acid	Ellagic acid- Mpro	-7.3				Umar *et al*., 2021
	Catechin	Catechin - Mpro	-7.2				
M. oleifera Lam	Chlorogenic acid	Chlorogenic acid- Mpro	-7.2				
Nigella sativa L.	Nigellidine	Nucleocapsid -(QHD43423)- nigellidine	-6.6			-0.3	Maiti *et al*., 2020
		IL1R_1itb (Nigillicine)	-6.23			-0.28	
		NSP2-(QHD43415_2)	6.24/			-0.28	
		Main protease_6lu7	6.38			-0.29	

Table 1. (Cont'd.).

Plant	Bioactive compound	Mechanism/Receptor ligand complex	Binding-energy (kcal/mol)	MM-GBSA	MM/PBSA	Ligand-efficiency	Reference
Ocimum sanctum L.	Vicenin	Vicenin - Mpro	8.97				Shree *et al*., 2020
	Isorientin 4' -O-glucoside 2''-O-p-hydroxy- benzoagte	Isorientin 4' -O-glucoside 2''-O-p-hydroxy- Mpro	8.55				
	Ursolic acid	Ursolic acid- Mpro	8.52				
	Amarogentin	Amarogentin - RdRp	-7.4		-39.38±0.79		Kar *et al*., 2022
		Amarogentin - -2Mpro	-8.0		Not stable		
Panax ginseng	Ginsenosides	Ginsenosides-Mpro	-9.63	-0.3			Garg *et al*., 2020
Rheum palmatum	Rhein,	Rhein - Mpro	-8.9				Narkhede *et al*.,2020
Silybum marianum (L.) *Gaertn*	Silybin	Silybin -Protease (PDB ID: 6W63)	-11.928				Prasanth *et al*., 2020
		Silybin- Spike glycoprotein – ACE-2 (6M0J)	-10.572				
		Silybin- RNA-dependent RNA-polymerase 6M71)	-11.499				
Tinospora cordifolia (Willd.) Miers	Tinocordiside	Tinocordiside- Mpro	8.10				Shree *et al*., 2020
Withania somnifera L. Dunal (Ashwagandha)	Withanoside II	Withanoside II - Mpro	-11.30	-62.50 ±5.25			Tripathi *et al*., 2020
	Withanoside IV	Withanoside IV- Mpro	-11.02	-81.29 ±4.78			
	Withanoside V	Withanoside V-Mpro enzymes.	-8.96	-87.01 ± 5.01			
	Sitoindoside IX	Sitoindoside IX- Mpro enzymes.	-8.96	-49.90 ± 4.15			
	Withaferin A	Withaferin A- Protease (6W63)	-11.242				Prasanth *et al*., 2020
		Withaferin A- Spike glycoprotein – ACE-2 6M0J)	-9.631				
		Withaferin A- RNA-dependent RNApolymerase 6M71)	-9.27				
	27-Deoxy-14-hydroxywithaferin A c4	27-Deoxy-14-hydroxywithaferin A c4- Mpro	-10.8		- 14.13		Parida *et al*., 2020
	27-Hydroxywithanone c37	27-Hydroxywithanone c37- Spike protein (PDB ID: 6lzg, chain B)S1	-8.74		-14.14		
	17-Hydroxywithaferin c6	17-Hydroxywithaferin c6- Mpro	-10.8		-23.15		
	12-Deoxy withastramonolide c40	12-Deoxywithastramonolide c40-Spike protein (PDB ID: 6lzg, chain B)S2	–8.27		-16.34		
	2,3-Dihydrowithaferin A c41	2,3-Dihydrowithaferin A c41 Spike protein (PDB ID: 6lzg, chain B)S4	7.45		-20.93		
	Withanolide R c10	Withanolide R c10- Mpro	-9.63		-15.293		Shree *et al*., 2020
	Withanoside V	Withanoside V - Mpro	10.32				
	Somniferine	Somniferine- Mpro	9.62				

Table 2. Docking Score of various bioactive compounds against Main protease_6lu 7/M^{pro}/$3CL_{pro}$, PLpro, RdRp, spike protein and ACE-2 of SARC-COV2* (Gowrishankar *et al*., 2021; Shawky *et al*., 2020).

Traditional medicinal plant	Bioactive compound	6LU* 7/M^{pro*}/$3CL_{pro*}$	PLpro*	RdRp*	Spike protein	ACE-2*
		Docking Score				
A. hierochuntica L., *Glycyrrhiza glabra* L.	Rutin	-12.632				
Cicer arietinum L.	Astragalin 6'O- diglucoside	-10.684				
Epilobium hirsutum L.	Myricetin3-O-glucuronide	-11.015				
Eruca sativa Mill.	Isoquercitrin			-9.785		
Eucalyptus globulus Labill.	Apigenin-7-O-glucuronide	-9.1	---	-8.8	-7.2	-8.8
	Ellagic acid	-8.4	---	-7.8	-6.2	-8.4
Glycyrrhiza glabra L.	Rocymosin B	-11.844	-10.593	-9.361		
	Glychionide A		-10.832			
	Isoliquiritin	-11.412		-9.732		
	Glucoliquritin apioside					
	Glabrene	-11.363				
	Glycyrrhizic acid			-9.611		
	Licoagroside A		-10.201			
	Rhamnoliquiritin			-9.484		
	Dihydrohaponiticin		-10.035			
	Oroxindin		-10.027			
Hibiscus sabdariffa L.	Cyanidin3,5-diglucoside	-10.658		-9.754		
	Delphinidin3-sambubioside	-11.061				
Justicia adhatoda L.	Vasicolinone	-8.0	---	-7.6	-6.4	-7.5
	Anisotine	-7.4	----	-8.2	-6.4	-7.8
Lepidium sativum L., *Tribulus terrestris* L.	Kaempferol-3,7-rutinoside	-10.88				
Medicago sativa L.	Kaempferol-3,7-glucuronide					
Olea europaea L.	Verbascoside	-11.721	-14.041			
	Mono(3,4- dihydroxycinnamoyl tartaric acid (caftaric acid)		-11.148	-10.66		
	Luteolin7,4'-diglucoside		-10.18			
	Paeonidin-3-rutinoside	-10.762				
	Cyanidin-3-rutinoside	-10.695				
Phyllanthus emblica L.	Eriodictyol 7-o-sophoroside		-10.338			
	1,6-di-O-galloyl-beta-D-glucose		-10.225			
Vitex negundo L.	Eudesmol	-8.0	---	-7.2	-6.0	-7.1
	Eudesmol	-7.4	---	-6.6	-5.8	-7.3
Schinus molle L.	Isoduercitrin 4"-rhamnoside	-10.892				
	Hyperin	-10.831				
Tribulus terrestris L.	Isoorietin 6-O"-beta-D-glucopyranoside			-9.797		
	Terrestric acid			-9.527		
	Quercetin-3-gentiobioside			-9.278		
Trigonella foenum-graecum L.	Fenugreekine			-9.894		
	Luteolin-8-C-beta-glucopyranoside			-9.493		

Main protease_6LU 7* Protein Data bank ID is 6LU 7, M^{pro} *main protease,$3CL_{pro}$, 3-chymotrypsin like protease, PLpro*, Papin like protease, RdRp*, RNA dependent RNA protease, spike protein and ACE-2* Angiotensin Converting Enzyme 2, SARC-COV2* severe acute respiratory syndrome coronavirus-2

Table 3. Clinical Trials of potent Traditional Medicinal Plants with antiviral and Immunomodulatory/Anti- inflammatory properties against pathogenesis of SARC-COV2.

Scientific name/Family/	Inclusion criteria	Exclusion criteria	Study design	Mechanism/ Outcome	Reference/ status
Artemisia annua L./ Asteraceae,	22 SARC-COV2 infected persons of both gander in age ranged18- 65 years, with mild to moderate disease Patients who are not utilizing any other drugs except supportive care	Severe and critical COVID-19 or admitted in ICU, age > 60 years, comorbidities (chronic heart, lung immune-compromised infection or on immune suppression medications. Severe and critical COVID-19. or pregnant women, or on anti- COVID therapy	Parallel assignment of double blind randomized controlled clinical trial	Main findings included coronavirus shedding from patients with negative results in first 6 days of treatment with Artesunate (duration of patient stay at hospital). Secondary finding comprised of total patient's no. admitted in ICU within 14 days of intervention (Fall in morbidity and mortality) and disappear of coronavirus manifestations in 6 - 10 days of intervention	Kapepula *et al*., 2020; Haq *et al*., 2020 **Not completed yet**
(*Asparagus racemosus* Willd / Asparagaceae), (*Zingiber officinale*/ Roscoe (*Embelia ribes* Burm.f / Primroses), (*Glycyrrhiza glabra* L./ Fabaceae), (*Terminalia chebula* Retz / Combretaceae), (*Tinospora cordifolia* (Willd.) Miers / Menispermaceae), (*Emblica officinalis* Gaertn./ Phyllanthaceae), (*Piper longum* L./ Piperaceae)	72 Covid-19 patients, 39 in intervention group and 33 in placebo group, both male and female (p=0.336) in age above 18 years, with mild to moderate disease from last 10 days. 52 patients (21 from placebo and 31 from IP) had qRT-PCR before start of trial and at 4th day	Pregnant or lactating women, symptoms of acute respiratory tract infection for more than seven days, diseased from 12 days, participant of any other clinical trial, serious / long-standing co-morbid conditions	Parallel assignment of single Centre, double blind, randomized controlled (1:1) clinical trial	C reactive protein test showed 50% reduction in CRP drug arm D Dimer test was not performed due to inadequate samples. Safety analysis (Liver Function Test and Kidney Function Test) proved that drug is safe with minimal drug-drug interactions. Numerical Rating Scale (NRS) present picture of infection intensity) and WHO ordinal grade significantly reduced in first four days (4.3± 1.13 to 1.74 ± 1.03; P< 0.0001) in both IP1 and IP2 arm. While in placebo arm numerical rating scale result (4.26 to 3.16 with P value less than 0.0001) also decreased but variation between IP and control group IP group results were highly significant statically. IP group showed significant decline in viral load (from 662081 copies /mL to 48963copies/mL on 4th day P=0.002) however in control group viral clearance is greater than 5 fold on 4th day (P= 0.106) in control arm. Retrospective score of IP treatment arm (p=0.023) while in in placebo and SoC[1]+ IP group (n=21) (p= 0.098). Effectiveness of herbal formulation to restore normal immune function after infection - TH1response was prominent in IP (P=0.023) not in control group (P=0.098), showing immune-dilatory effect of medicine. TH2 respond similarly in both groups. Variations in absolute NK Cells in control (p=0.020) but not in drug arm (p=0.067). Although variation magnetite was high in IP as compared to control. Prominent intensification in absolute CD3 CD4 & CD8, absolute B cells count, T helper cells noticed in both groups. Immunoglobulin IGG(Serum) reduced significantly in both groups while Immunoglobulin IGM (Serum) was non-significant in both groups at 30th day of investigation. Results of IGG antibodies were statistically non-significant but observed antibodies level was 20 % higher in IP arm. Ability of herbal formulation in diminishing the after effects of infection, C reactive protein test showed 50% reduction in CRP drug arm however, placebo arm showed increase amount of it. D Dimer test not performed due to inadequate samples. Safety profile (LFT and KFT) proved that drug is safe with minimal drug-drug interactions	Rangnekar *et al*., 2020; Patankar *et al*., 2022 **completed**
Azadirachta indica A. Juss or *Hypericum* L. oil	128 participants both male and female patients age 18 years or above with COVID-19 positive having symptoms of upper respiratory infection	Patients with severe symptoms of respiratory infection Pneumonia, r hospitalized or Asymptomatic, history of asthma, allergic to Neem /Hypericum oil & Pregnant females and COVID infected persons with comorbidities/ on regular inhalation were excluded	Parallel assignment of double blind randomized controlled clinical trial	Primary of the trial is required duration for complete resolution of signs & symptoms report in participants / group, Number of participants admitted to clinic due to deterioration of their condition per group Secondary Outcome Measures includes: required duration for reduction in signs & symptoms report in participants / group along with all adverse/ side effects reported/group [Time Frame: 28 days]	NCT04357990 (2020) **Recruiting**
Glycyrrhiza glabra L. / Fabaceae	60 (SARS)-(CoV-2) patients both gander age ≥18 y with weight ≥ 35 kg with moderate disease already Hospitalized before ≤48 hours.	Subjects history of allergy to Licorice, comorbidities (chronic heart, hypertension, kidney & liver failure. Severe /critical Covid-19 patients. Utilizing antibiotics, SSRIs[1], MAOIs[2], diuretics, corticosteroids, and antiarrhythmic drugs. Taking any antiviral drug in one month before trial.	Parallel- assignment of open-label randomized controlled clinical trial (1:1 ratio)	Time duration to recover from clinical manifestations, like pyrexia, dry cough, and fatigue, auxiliary to para-clinical characteristics (thrombocytopenia, lymphocytopenia, and C-reactive protein) assessed as main finding. However, secondary finding included evaluation of time duration for recovery of clinical and para-clinical characteristics and duration of hospital stay, besides adverse events rate in study group. Both primary and &secondary findings duration is 1 week.	Safa *et al*., 2020a **Not completed yet**

Table 3. (Cont'd.).

Scientific name/Family/	Inclusion criteria	Exclusion criteria	Study design	Mechanism/ Outcome	Reference/ status
Glycyrrhiza glabra L./ Fabaceae), *Nigella sativa* L. / Ranunculaceae	200 patients with mild-moderate COVID-19 adult (25 - 40 years old). Study is divided as: (Vitamin D & Nigella sativa: Vitamin D, Nigella sativa and Indian Costus: Vitamin D s Nigella sativa s Quinine: Vitamin D Nigella sativa & Anise seed: Vitamin D Nigella sativa and Deglycyrrhizinated Licorice: control)	Pregnant or lactating women, End-stage respiratory tract infection, participant of any other clinical trial, serious / long-standing co-morbid conditioned patients were excluded from study	Sequential Assignment Randomized Controlled Parallel 6 arm- double blind Clinical Trial	This trial measures includes Respiratory indexes & duration of stay in clinic under observation of doctors [finding duration 10 Days], time of Clinical improvement, Infection reduction of respiratory tract scanning test like CT/ X-ray, leukocytes in microliter correlated with mortality assigned duration for this finding is one month evaluation of time duration for recovery of clinical and para-clinical characteristics, recovery duration from pyrexia to normal [Assigned Time half month], measurement of C-reactive protein, iron level, Lactic acid dehydrogenase [Time Frame: 25 Days] Efficacy evaluation of herbal intake on Lipid profile [LDL, HDL, Total cholesterol] and total plasma antioxidant capacity after two weeks are also included in trial	NCT04553705 (2020) **Recruiting**
Honey & *Nigella sativa*/ Ranunculaceae	313 Covid-19 Moderate & severe Covid-19 hospitalized patients both male and female, age above 18 years, (156 control and 157 on HNS) both male or female, age above 18 years, 210 with moderate (107 in HNS & 103 control group) and 103 with severe (50 in HNS & 53 in placebo group)	Consent abstention, Pregnant and lactating mothers, allergic history to any medication used in this trial, critically ill patients or patient unable to take any food and liquid orally were excluded from trial.	Randomized controlled, clinical trial in 1:1 ratio at 4 centers in Pakistan.	Primary outcome measure comprised of recovery duration to COVID negative, severity of symptoms progression (categorization of infection based on depending upon the intensity of symptoms mild, moderate and severe) and length of Hospital admittance [Analysis period: 13 days]. Main results exhibited viral clearance (Required recovery time to get COVID-19 negative) occurred four days' sooner in both moderate and severe diseased groups of HNS with P<0.0001. Severity of symptoms progression [Analysis period: 13 days] reduce up to 50% 4 versus 7 days in moderated, and 6 against 13 days in severely diseased participants. HNS group Medical Grade rank [Analysis period: 0, 4, 6, 8, 10 and 12 days] on 6th day showed resumption of normal activity in more than sixty percent (63.6% against 10.9%) moderate COVID-19 participants (P<0.0001). However, in severely diseased COVID-19 exhibited hospital discharge fifty percent vs 2.8% (P<0.0001). Severe COVID-19 HNS arm mortality rate [Analysis period: 30 days] recorded quarter-fold lesser in HNS medicinal plants intervention group than control (4% Vs 18.87%) (P=0.029). Secondary outcome revealed that average oxygen saturation at room air [Analysis period: 13 days] was greater than ninety percent, in HNS severely infected cases and recorded results on 6th days (p< 0.0001). Noteworthy reduction in fever degree was notified after four days (P=0.0001), CRP were lowered after six days (6.15 ±2.45 in moderately infected group and 9.44± 4.97mg/L in control, and severely infected group 15.83vs control 23.32mg/L). No HNS-related adverse effects observed	Ashraf *et al*., 2020 **Completed**
Honey & *Nigella sativa* L. / Ranunculaceae	1000 asymptomatic both male and female COVID-19 patients age above 18 years will be tested if they have had 4 days after contact with infection person.	Pregnant or lactating women, participant of any other clinical trial, serious / long-standing co-morbid conditions Multi-organ failure active COVID-19 were excluded.	Parallel assignment randomized, controlled Quadruple blinding clinical trial (1:1 ratio)	Primary includes prevalence of COVID-19 cases during two-week trial. In addition to it prevalence of infection linked signs & symptoms, hospital admission duration, and demise related to severity of infection manifestations during two-week trial.	NCT04767087 (2021) Ashraf *et al*., 2021 **Recruiting**
Nigella sativa L. / Ranunculaceae	200 patients of both gander man and women with mild COVID-19 adult (18 - 65 years old).	Subject history of allergy to nigella sativa, Severe and critical Covid-19 Severe chronic kidney, liver, breast feeding or Pregnancy, or expected shifting of patient to other hospital within 3 days of infection were excluded from trial	Parallel- assignment randomized controlled (1:1 ratio), open-label, clinical trial	Clinical recovery ratio of patients (retrieval of infection symptoms completely) during 2 weeks of trial.	Koshak *et al*., 2020 **In Execution Phase**
Nigella sativa L. / Ranunculaceae	100 cases with mild-modest COVID-19 of both gander male and female age ranged (18 - 65 years). Study is divided in to 1-4 group (each with 25 patients): 1 is control, remaining 3 groups are intervention Groups (Nigella Sativa: vitamin D3: Nigella Sativa & vitamin D3: Control)	Asymptomatic, severe and critical Covid-19 patients need ICU. Severe chronic organ (kidney, liver) active COVID-19, breast feeding or Pregnant Women Allergic persons to *Nigella sativa* were excluded.	Parallel- Quadruple assignment randomized controlled (1:3 ratio), open-label, clinical trial	Evaluation of safety profile and effectiveness of black cumin and vitamin D intervention for elevation of all sign and symptoms of coronavirus infection Assigned duration was half month. time duration for recovery of clinical and para-clinical characteristics, recovery duration from pyrexia to normal [Assigned Time half month], measurement of C-reactive protein, iron level, Lactic acid dehydrogenase ICU admittance rate of patients [Time Frame: 25 Days] Efficacy evaluation of herbal intake on Lipid profile [LFT. KFT, ESR, CBC] prothrombin time, partial thromboplastin time in seconds, conformation test of lungs status both CT chest and PCR after two weeks were also included in trial.	NCT04981743 (2021) **In Execution Phase**

Table 3. (Cont'd.).

Scientific name/Family/	Inclusion criteria	Exclusion criteria	Study design	Mechanism/ Outcome	Reference/ status
Nigella sativa L. / Ranunculaceae	60 SARS-CoV-2 positive participants both man and women age above 18 years without serious complications due to viral infection able to take oral medication on their own.	Subjects history of allergy/ hypersensitivity to any of medicinal herb of "Ayurveda" chronic heart, kidney & liver failure or hypertension, Severe /critical Covid-19 patients. Taking any antiviral drug in one month before trial. breast feeding or Pregnant Women were excluded from study	Parallel- assignment randomized controlled (1:1 ratio), open-label, clinical trial	Average time duration required to Constant Experimental Response [duration of investigation 21 Days] Safety profile of Investigational Product in patients [duration of investigation Day 45] Measureable variation in Viral Load representing reduction in viral content also evaluation of Viral Clearance. Effect of Ayurveda on harshness and Transformation in Sign & symptoms of SARS-CoV-2 along with Connection between infection Symptoms and Viral Load within 2 weeks of trial initiation	NCT04914377 (2021) **In Execution Phase**
Nigella sativa L. / Ranunculaceae	500 participants with mild-moderate COVID-19 adult (40 - 70 years old). 500 patients are divided into 2 non-homogenous groups outpatients & Ambulatory patients or inpatient	COVID-19 Patient currently in shock, with inflammatory bowel disease, chronic dysentery, breast feeding or Pregnant Women patient. Subjects history of allergy/ hypersensitivity to black cumin were excluded from study	Parallel- Quadruple-assignment Randomized Controlled Blind Label Clinical Trial	Primary evaluations include the evaluation of Respiratory infection in SarsCOV2 Secondary Outcome Measures includes contamination of the entourage in the event of respiratory infection by COVID19 [Time Frame: one month]	NCT04914767 (2021) **In Execution Phase**
Tinospora cordifolia / Menispermaceae (Piper longum)	26 participants both male and female patients age ranged from 20 to 70 years with mild to moderate COVID-19 positive, not taking any other medication in trial duration	Positive cases with ongoing immunosuppressive therapy due to organ transplantation, autoimmune diseases or cancer, exposed to HIV infection, or patient with any comboridies need instant medication, Pregnant and lactating female were also excluded from study	Single Group (Open Label) Supportive Care clinical trial	Time duration required for elevation of COVID-19 manifestations described by subjects. Effect of formulation in inhibition of critical stage of Covid19 infection in study subjects within 2 weeks of trial initiation. Side effect/ adverse events of herbal formulation faced by no. of subjects and evaluated with AiM COVID-19 App, how many subjects hospitalized due COVID-19 rigorousness and recovery duration back to normal life activity after negative RT-PCR [investigational Time duration: Up to 14-days]	NCT04621903 (2020) **In Execution Phase**
Tinospora cordifolia / Menispermaceae	91 asymptomatic patients, when admitted to hospital age ranged 18 -75 (years) both gander man & women	Subjects with age above 75 years, mild-moderate COVID-19 sign & symptoms at time of hospitalization. Taking any antiviral drug in one month before trial were excluded from study	Cohort Retrospective Observational clinical trial (1:1 ratio)	Control group showed 11.7% modest sign & symptoms after mean 1.8 days while experimental group taking Ayurveda didn't describe any sign / manifestation. Results showed measurable change of virus clearance in subjects taking Guduchi Ghan Vati (n=40) (97.5%) and patients not taking any Ayurveda and in standard care (n=51) after one week (15.6%) and recorded p value is 0.000, and after two weeks 100% viral removal in subjects with Ayurveda while 82.3% was recorded in control group. Similarly, significant difference was also recorded in length of hospital stay in Ayurveda group (6.4 day) in comparison with control (12.8 days) ($p< 0.0001$).	NCT04480398 (2020) **Results published** Kumar *et al*., 2020
Tinospora cordifolia / Menispermaceae	46 COVID-19 Patients of any age greater than 18 years asymptomatic at the time of hospitalization	Subject showing symptoms relating to Covid-19 or having Severe nausea, critical cases of COVID-19 need ventilator to sustain life. Subjects with kidney or liver failure or comboridies were excluded from study	Single Group Assignment Open Label Clinical Trial	Primary includes prevalence of COVID-19 clearance during two-week trial. In addition to it prevalence of infection, hospital admission duration, adverse effects linked with Guduchi Ghan if any reported by test subjects. and lab test results related to infection manifestations during two-week trial	NCT04542876 (2020) **In Execution Phase**
Tinospora cordifolia/ Menispermaceae	216 participants both male & female of age ranged18 to 60 Years Household contact (without social distancing) residing with the infected person for two weeks before diagnosis. Connecting for help through internet / telephone	Currently hospitalized –with major Signs of modest or critical covid-19 like pyrexia, cough, or breathing issue or having comboridies of any health issue which need immediate therapy.	Parallel- assignment Non-Randomized Open Label Prevention clinical trial	**Primary evaluation** includes: Total subjects of with active coronavirus infection PCR- proven [Time Frame: 14-days] **Secondary Outcome** Measures includes: Time to start of symptoms of COVID-19 & overall Severity disease (zero symptoms; 10 = maximum severity within two weeks of trial initiation.	NCT04920773 (2021) **In Execution Phase**

Table 3. (Cont'd.).

Scientific name/Family/	Inclusion criteria	Exclusion criteria	Study design	Mechanism/ Outcome	Reference/ status
Zingiber officinale/ Roscoe officinale (Ginger)	84 Covid-19 positive subjects of both gander man or women in age ≥18 years, weight ≥35 kg with moderate disease admitted to Hospital ≤48 hours	Subject history of allergy to Ginger, comorbidities (chronic heart, kidney, liver failure damage, & hypertension sufferer critical stage of Covid-19 infection SSRIs, MAOIs, Pregnancy and breastfeeding were excluded	Single center Parallel-assignment Randomized controlled double-blind, clinical trial (1:1 ratio)	Findings of Prime importance are retrieval rate of COVID-19 symptoms, comprising pyrexia, dry cough, fatigue, and disturbance of GI tract along with Para clinical attributes, like thrombocytopenia, lymphocytopenia, and C-reactive protein during first week of trial. Study also included duration of recovery from clinical and para-clinical symptoms. In addition to it, secondary findings of this trial included frequency of severe adverse event during the randomization period of a week.	Safa *et al*., 2020b **Completed**
Zingiber officinale/ Roscoe (Ginger), lemon, honey, *Curcuma longa* L. / Zingiberaceae (turmeric)	18 Covid-19 Patients of both gander man and women age ranged 18 -60 years with sign & symptoms of, pyrexia, flue, any one sign from following; cough, nasal obstruction, sore throat) along with one manifestation of fatigue or headache from last two days.	Subject showing symptoms relating to sever/ critical Covid-19 need ventilator to sustain life or having Severe nausea, Subjects with kidney or liver failure or comboridies, breast feeding or Pregnant Women patient. Subjects history of allergy/ hypersensitivity to black cumin were excluded from study	Single Group Assignment Open Label Supportive Care clinical trial	Primary Outcome is Measurement of Time to achieve afebrile < 37.2°C) Secondary Outcome is Measurement of Severity of influenza symptom score two times a day within first week of intervention.	NCT04345549 (2020) **In Execution Phase**
Withania somnifera (L.) Dunal/ Solanaceae, *Tinospora cordifolia*/ Menispermaceae, *Ocimum tenuiflorum* L./ Lamiaceae	28 participants both male and female patients age ranged 20 - 70 years with mild or moderate COVID-19 positive proven through RT-PCR and not involved in another medication during trial	Subjects with severe/critical infection, requires Hospitalization or O_2 support or on immunosuppressive therapy or diagnosed active cancer diagnosis, or using any other antiviral medication Pregnant and lactating females are also excluded from study	Single Group, Assignment, (Open Label) Supportive Care, clinical trial	Findings of Prime importance are retrieval rate of COVID-19 to find out the effectiveness of therapy byAiM Covid App. Clinical finding of the subjects were also recorded with in two week of initiation.	NCT04716647 (2021) **In Execution Phase**

Another Clinical Trials with number NCT04387240 (phase 2 study) registered by Princess Nourah Bint Abdulrahman University Riyadh, Central, Saudi Arabia, to evaluate the antiviral effectiveness of *Artesunate* (*Artemisia annua* L.) in COVID-19 patients. For study group, (COVID-19 patients) *Artemisinin / Artesunate* 0.1 g once daily for 5 days. While placebo group received standard therapy without *Artemisinin / Artesunate* (Kapepula *et al*., 2020; Haq *et al*., 2020).

A clinical trial registered with no NCT04914377 by Novatek Pharmaceuticals to evaluate the safety and efficacy of TQ formula in COVID-19 participants (BOSS). Trial is in its recruiting stage at San Diego, California, Florida L & A Morales Healthcare Hialeah, Florida, Texas & United Memorial Medical Center Houston, Texas, United States. TQ formulation 3000 mg will be administered two time in a day orally (3 capsules of 500mg at one time). While control group will be kept on same amount of corn oil in capsules (NCT04914377, 2021).

A clinical trial registered with no NCT04981743 by Ain Shams University to evaluate the efficacy of Nigella Sativa versus Vitamin D_3 as supplement therapy in coronavirus disease 2019 (COVID-19). Trial is in recruiting stage at respiratory system specialized hospital at Kobry Elobba Military Medical hospitals Cairo, Egypt. Patients will be divided into four groups. Group 1 daily supplemented with 900 mg of Nigella Sativa in addition to standard care procedures in a day. Experimental group 2 was administered 2000 IU of vitamin D3 tablet once in a day. Experimental group 3 was kept on both Nigella Sativa 900 mg two times a day along with one dose of 2000 IU vitamin D3 tablet in day with standard care procedures and fourth group is control (NCT04981743, 2021).

A clinical trial registered with no NCT04914767 by Hôpital Universitaire Sahloul to evaluate the Nigella 5 by in the treatment of SARS COV2 (COVID-19) (Nigelle5). Trial has completed its recruitment phase and will be conducted at Hôpital Universitaire Sahloul HU Sahloul, sousse, Tunisia. 250 test subjects will take 100 capsules of black cumin: One capsule after fixed interval of two hours for first 3 days. From onward to next nine days, subjects will take one capsule, three times a day (NCT04914767, 2021).

A clinical trial phase 2/phase 3 registered with no NCT04553705 by Maternity and Children Hospital, Makkah University of Arizona and Beni-Suef University sponsored it, to evaluate Omega-3, Nigella Sativa, Indian Costus, Quinine, Anise Seed, Deglycyrrhizinated Licorice, Artemisinin, Febrifugine on immunity of patients with (COVID-19). Trial is in its recruiting stage at Beni-Suef University, Saudi Arabia, Makkah. Subjects were divided into six groups, five interventional and one control. Study group was kept on Omega-3 supplement 1000mg, 1g black seed oil, 1g Quinine, 450mg anise seed & Deglycyrrhizinated Licorice 800 mg in different combinations (NCT04553705, 2020).

A clinical trial phase 2/phase 3 registered with no NCT04767087 was conducted to evaluate prophylactic potential of honey and *Nigella sativa* L. against hospital and community-based SARS-CoV-2 spread: a structured summary of a study protocol for a randomized controlled trial at Shaikh Zayed Post-Graduate Medical Institute, Ali

Clinic and Doctors Lounge in Lahore (Pakistan). Test subjects will receive either raw natural honey (0.5 g) and encapsulated organic *Nigella sativa* seeds (40 mg) / kg body weight/ day while empty capsule with and 30 ml of 5% dextrose water will received by placebo for two weeks (NCT04767087, 2021).

A clinical trial phase 2/phase 3 registered with ID NCT04345549 to evaluate ayurveda self-management for flu like symptoms during the COVID-19 outbreak by NMP Medical Research Institute. Trial has completed its recruitment phase and will be executed at NMP Medical Research Institute & Padmanabhama & Ayurveda Hospital and Research Centre of Jaipur, Rajasthan, India in collaboration with Aarogyam Leicester, United Kingdom. 18 patients will be kept on lukewarm saline gargle, Steam inhalation, Paracetamol, plenty liquids and rest, Yoga breathing along with standard care at self-isolation place. Along with that, participants were advised to constitution based ayurveda treatment using herbs (Ginger/ lemon/ turmeric/ honey suggested as per individual), life style and yoga (NCT04345549, 2020).

A clinical trial was registered with ID NCT04716647 to evaluate feasibility of Ayurveda in patients with Mild-to-Moderate COVID-19: A community-based participatory research by Aarogyam UK. Trial has completed its recruitment status, will be executed in collaboration of Padmanabhama and Ayurveda Hospital and Research Centre of Jaipur, Rajasthan, India.28 subjects will be supplemented with different dosage of Ashwagandha (250 mg to 5 g), Giloy: (500mg to 1g), Tulsi (500mg-1g), according to age, weight and harshness of disease symptoms (NCT04716647, 2021).

ID NCT04920773 registered to evaluate community-based post-exposure prophylaxis for COVID-19 by Aarogyam Leicester, United Kingdom. Trial has completed its recruiting phase and will be conducted at NMP Medical Research Institute & Padmanabhama and Ayurveda Hospital and Research Centre of Jaipur, Rajasthan, India in collaboration with Aarogyam Leicester, United Kingdom. Experimental group will be kept on 500 mg of Samshamani vati or Giloy Ghanavati (Aqueous extract of Tinospora cordifolia) 2 times a day while control group will be on standard guidelines Practice (physical isolation, breathing and hand hygiene and wearing of mask) (NCT04920773, 2021).

A clinical trial conducted with ID NCT04357990 to evaluate effect of viruxal oral and nasal spray for treating the symptoms of COVID-19 (KONS-COVID19). Trial is in recruiting phase and will be conducted at Land spitalinn University Hospital, Iceland. Viruxal Oral and Nasal Spray is a Class I CE marked medical device manufactured by Kerecis hf (the "Device") used against recovery of COVID 19 patients. Subjects will be divided into experimental and control groups. Device comprises Omega3 Viruxide obtained from (Neem oil) *A. Indica* and St. John's Wort oil. The Device will be administered to the oral and nasal passages, three times per day to provide protection against viral infection (NCT04357990, 2020).

A clinical trial with ID NCT04621903 conducted a pilot study on efficacy and safety of ayurveda combination in patients with mild-to-moderate COVID-19: community based participatory research by University of Warwick, Aarogyam UK in collaboration with All India Institute of Ayurveda, Ministry of AYUSH, Government of India. Ayurveda "Shanshamani Vati Plus" was given as combination of Guduchi (*Tinospora Cordifolia*; 300 mg) and Pipli (*Piper Longum* 75 mg) twice daily (NCT04621903, 2020).

Conclusion

Novel SARS-CoV-2 pandemic needs the emergency of approved COVID-19 therapy. For this purpose, preclinical and clinical studies of traditional medicinal plants with their bioactive compounds might be effective agents and adjunctive treatment of COVID-19. Docking studies of different valuable bioactive compounds against structural, nonstructural proteins and human inflammatory proteins showed that these 43 TMP are capable to interfere with pathogenesis via inhibiting entry and replication of SARS-CoV-2 in host cells. Among those TMPS *Azadirachta indica* A.Juss, *Glycyrrhiza glabra* L., *Zingiber officinale* Roscoe, *Embelia ribes* Burm.f, *Terminalia chebula* Retz, *Tinospora cordifolia (*Willd.*)* Miers, *Asparagus racemosus* Willd., *Emblica officinalis* Gaertn., *Piper longum* L., *Nigella sativa* L. *& Artemisia annua* L. *Tinospora Cordifolia* (can cure fever, cough and common complications of COVID-19 via anti-inflammatory effects) were evaluated in clinical trials as an effective adjunctive compound in COVID 19. On the other hand, various medicinal plants and their bioactive compounds could serve as antiviral substances in prevention and cure of COVID-19 via, killing virus and modulate immune system. In this review, we collected up to date available molecular docking studies and clinical trials of potent bioactive compounds of TPMs in prophylaxis and anti-COVID therapy to enlighten the new compounds for further consideration in drug discovery.

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