



Scientific rationale of Indian AYUSH Ministry advisory for COVID-19 prevention, prophylaxis, and immunomodulation

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Abstract

The current outbreak of COVID-19 is caused by the SARS-CoV-2 virus that has affected > 210 countries. Various steps are taken by different countries to tackle the current war-like health situation. In India, the Ministry of AYUSH released a self-care advisory for immunomodulation measures during the COVID-19 and this review article discusses the detailed scientific rationale associated with this advisory. Authors have spotted and presented in-depth insight of advisory in terms of immunomodulatory, antiviral, antibacterial, co-morbidity associated actions, and their probable mechanism of action. Immunomodulatory actions of advised herbs with no significant adverse drug reaction/toxicity strongly support the extension of advisory for COVID-19 prevention, prophylaxis, mitigations, and rehabilitation capacities. This advisory also emphasized *Dhyana* (meditation) and *Yogasanas* as a holistic approach in enhancing immunity, mental health, and quality of life. The present review may open-up new meadows for research and can provide better conceptual leads for future researches in immunomodulation, antiviral-development, psychoneuroimmunology, especially for COVID-19.

Keywords COVID-19 · Indian AYUSH advisory · *Ayurveda* · Immunomodulation · Therapy

Introduction

Today whole world is battling with the current pandemic of COVID-19 (Corona Virus Disease-2019). Increasing patient trend, high extend of spread, the unpredictability of manifestation of the clinical disease spectrum, and the uncertainty of cure are some worrisome concerns behind such social and mental stress in COVID-19. Information on COVID-19 is evolving very fast and it unlikely to have any definite treatment in near future. Drug discovery is a costly and large gestational affair while repurposing can cut short both cost/gestational time and bypass the pre-clinical and safety studies hence a push for Hydroxychloroquine repurposing is emphasized and exhibiting with a mixed response from scientists and clinicians (Rodrigo et al. 2020). Amid such situations, where modern medical science and traditional medicine are standing on the same platform, we must explore all possibilities to prevent, mitigate, and control this pandemic. It is the right time to integrate critical care and complication management skills of allopathy and preventive, immunomodulatory, and mental health management through traditional medicine. The development of traditional medicine with the perspectives

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of safety, efficacy, and quality would help not only to preserve the traditional heritage but also to rationalize the use of herbal medicine in human healthcare (Mukharjee et al. 2017). Integration of traditional Chinese medicine and modern medicine had formed the dominant treatment strategy in all COVID-19 affected areas across China (Jia and Yunfei 2020). Following a rich heritage of traditional medicine, the Indian AYUSH (Ayurveda, Yoga, Unani, Sidha, and Homeopathy) ministry has released an advisory for preventive health and immunity-boosting measures for self-care during the COVID-19 crisis (<https://ayush.gov.in>). It underscores the concept of “Prevention is better than cure”.

The author has screened the capacity of AYUSH-advisory in the prevention, prophylaxis, mitigations, and rehabilitation of COVID-19 cases. Advisory broadly divided into 3 categories i.e. general measures, immunity promotive measures, and the Ayurveda procedures to follow. General measures of advisory advocate drinking warm water throughout the day in COVID-19 outbreak and practice of *Yogasana*, *Pranayaam*, and *Dhayana* (meditation) for 30 min daily (<https://ayush.gov.in>). According to Ayurveda, drinking hot water helps in digesting *Aama* (a pro-inflammatory marker of impaired metabolism) followed by *Samprapti Vighatan* (break of disease cascade). It is advocated in *Naveen Jwara* (fever) (Vaidya and Trikamji 2004). It is a good natural remedy to treat nasal congestion. A clinical study done in 15 healthy subjects, the nasal mucus velocity was measured before and at 5 and 30 min after drinking hot water increased from 6.2 to 8.4 mm/min five minutes after administration in patients drinking hot water by sip, again value returned to their baseline at 30 min. The above study concludes increased nasal mucus velocity might be helpful in the management of upper respiratory tract infections (Saketkhoo et al. 1978).

On the line of advisory, the author emphasized how *Yoga*, *Dhyana*, and *Pranayaam* practices can be helpful in fighting psychoneuroimmuno perturbation during COVID-19. Among general measures, *Yoga* therapy is a form of mind–body medicine that integrates an individual’s physical, psychological, social, and spiritual components to enhance health, with a primary focus on stress and related illnesses (Atkinson and Permuth-Levine 2009). *Yoga* therapy comprises yogic physical postures (*Asanas*), *Yogic* breathing techniques (*Pranayama*), meditation (*Dhyana*)/Mindfulness, *Yogic* cleansing techniques (*Kriya*), *Yogic* gestures (*Mudras*), and locks (*Bandhas*) (Sengupta 2012). Evidence suggests *Yoga* as a therapeutic tool in alleviating fear, depression, anxiety, negative thinking, and enhance the quality of sleep (Cabral et al. 2011). With mounting scientific literature/research in the field of *Yoga*, it is regarded as a form of Complementary and Alternative

Medicine (CAM) by National Centre for Complementary and Integrative Health (NCCIH), USA.

Spices like *Curcumin longa* Linn. (*Haldi*), *Cuminum cyminum* Linn. (*Jeera*), *Coriandrum sativum* Linn. (*Dhaanyaka*), and *Allium sativum* Linn. (*Lahsun*) are recommended for cooking. Herbal medicines like *Ocimum sanctum* Linn. (*Tulsi*), *Piper nigrum* Linn. (*Maricha*), *Dry Zingiber officinale* Roscoe (*Shunthi*), *Cinnamomum* species (*Tvaka*), *Dry Vitis vinifera* Linn. (*Munnaka*, Raisin, dried grapes) are recommended to make herbal tea/decoction and consume twice daily. *Chyawanprasha* (Herbo-mineral ayurvedic preparation) 10 g daily in the morning is also advised (<https://ayush.gov.in>). Herbal drug screening revealed the presence of phytoconstituents such as polyphenol, terpenoid, flavonoid, curcumin, anthocyanin, proteins like lectins or agglutinins, piperine, vitamin C, gingerols, anthraquinone, and so on. These phytochemicals showed wide pharmacological actions but here we are documenting immunomodulatory, antiviral, and antibacterial actions, co-morbidity preventive action, and their probable mechanism of action.

The third section i.e. Ayurvedic procedures advocates oil pulling therapy (*Kawala*) by sesame or coconut oil for 2–3 min followed by the warm water rinse, nasal application (*Pratimarsh Nasya*) of sesame oil or coconut oil or *ghee* in morning and evening. Daily steam inhalation with *Mentha arvensis* Linn. (*Pudina*) or *Trachyspermum ammi* Linn. (*Ajwain*), and *Syzigium aromaticum* Linn. (*lavang*) powder with honey orally is advised for ailment like sore throat or cough (ayush.gov.in). Recently, Indian states like Kerala, Delhi, Gujarat, Goa, and so on, allowed to treat COVID-19 confirm cases through dedicated Ayurveda/integrative approach using Ayurveda and modern medicine through projects like ‘*Sukhayusham*’, ‘*Swasthyam*’, and ‘*AyurRaksha*’ clinics. The herbal medicines and Ayurveda procedures mentioned in the advisory are being used for the purpose of immunomodulation, antimicrobial, and stress management in various traditional medicine the system of the world since ancient period (Table 1). In the next section, AYUSH recommended herbs, their present antimicrobial, immunomodulatory, and antiviral actions are discussed in detail and how these medicines and procedures are vindicated in retaliation of COVID-19.

Immunomodulatory and antimicrobial actions of herbs advised by Indian Ayush Ministry

The current advisory supports the scientific background of Ayurvedic plants and their phytochemicals support the immune system and have antimicrobial action (Fig. 1a,b). Apart from that, we have also discussed the detailed role of advised herbs because each phytochemical influences

Table 1 Immunomodulatory actions and traditional uses of herbal drugs as per Indian AYUSH guidelines

Herb name	Traditional uses	Study/study model	Preparation (dose)	Results	References
<i>Rasona (Allium sativum)</i>	Athletes for increasing stamina during the earliest Olympics in Greece. (2) Oil as an antimicrobial in <i>Ayurveda</i> . (3) In Turkish traditional medicine cloves and bulb of garlic as an immuno-tonic, antelmintic, ringworm management, cardio-protective and rheumatism	In vivo study, BALB/c mice In vitro study, tumor cells, S180 sarcoma cell line In vivo study, Broiler chicks	Aged garlic extract (AGE) (10 µl/kg/day/I.p. route) Diallyl trisulfide (DATS) higher concentration dose (50 µg/ml) DATS lower concentrations dose (3–12.5 µg/ml) Garlic or ginger dietary supplementation (garlic extract at concentrations of 10–15% and ginger extract at a concentration of 15 g/kg diet)	Protective Altering of cytokine production through raised levels of IFN-γ and IL-4. Reduced lymphocytes in the spleen T cell proliferation inhibition Augmented the proliferation of T cells to Con A Innate immune response modulated via phagocytosis augmentation, bactericidal activity enhancement, and nitric oxide production reduction with triggering the IL-1β, IL-6, and IFN-γ cytokines expression	Larypoor et al. (2013) Feng et al. (1994) Elmowalid et al. (2019)
<i>Jiraka (Cuminum cyminum/ Nigella sativa)</i>	Hoarseness, jaundice, leprosy, chronic diarrhoea, bronchopulmonary disorders, and as a cough remedy. (2) Bloody diarrhoea, inflamed eczema, and headache in Indonesia. (3) In <i>Unani</i> system of medicine, used for the treatment of ulcers, boils, stye, and cough. (4) Used to treat pneumonia in Russia. (5) gastrointestinal, gynecological, and respiratory disorders in Iranian traditional medicine	Cyclosporine-A immune-suppressed Swiss albino mice Ovalbumin-induced allergic diarrhea in BALB/c mice BALB/c mice Typhoid vaccination challenged long Evan rat model Pigeons (<i>Columbalivia</i>) Broiler chicks (Ross 308)	<i>Cuminum cyminum</i> seed powder (25, 50, 100 and 200 mg/kg) <i>Nigella sativa</i> seed hexanic extract and thymoquinone (intragastric gavage once a day for 4 days) Methanolic extract of <i>N. sativa</i> (sublethal dose- 20 mg/dose/animal/I.p.) <i>N. sativa</i> seed oil Co-administration of <i>N. sativa</i> (2.5%) with oxytetracycline (OXT) (0.05 g/kg of feed) Seed extract (750, 1000 ppm) in drinking water + control diet without coriander	A dose-dependent increase in CD4 and CD8, and Th1 predominant immune response Improved symptoms and immune parameters Protective increase in total WBC count, increased spleen weight, and enhanced splenocyte proliferation Decreased antibody production with decreased splenocytes and neutrophil counts Blocks the inhibitory effects on TLC and lymphocyte counts IgG antibody against sheep red blood cells improved, IgM was higher in fed animals	Chauhan et al. (2010) Duncker et al. (2012) Ghoniemi et al. (2011) Ahmad et al. (2013) Al-Ankari (2005) Hesam et al. (2014)
<i>Dhaanyaka (Coriandrum sativum)</i>	(1) Juice of fresh leaves used as a gargle in sore throat and stomatitis. (2) Seeds are used for the treatment of fever and diarrhea. (3) A decoction of leaves used in conjunctivitis				

Table 1 (continued)

Herb name	Traditional uses	Study/study model	Preparation (dose)	Results	References
<i>Tulsi</i> (<i>Ocimum sanctum</i> , <i>Ocimum basilicum</i> , <i>Ocimum americanum</i>)	(1) A decoction of leaves is a remedy for cold. (2) As prophylaxis against malaria, fresh <i>Tulsi</i> leaves with black pepper in the morning	Male Wistar rats, male Swiss albino mice, and guinea pigs	<i>Ocimum sanctum</i> seed oil (3 ml/kg/i.p.)	Modulates GABAergic humoral and cell-mediated immune response	Mediratta et al. (2002)
		Wistar albino rats infected with LD50 dose of <i>S. typhimurium</i> infection	Aqueous extract of <i>O. sanctum</i> leaves (250 mg/kg)	Increased number of <i>S. typhimurium</i> engulfed peritoneal macrophages An elevated level of TNF- α , IFN- γ , and IL-2 cytokines in serum	
		60 crossbred lactating cow sub-clinical mastitis (SCM)	Aqueous extract of <i>O. sanctum</i> leaf (100 mg/teat/intramammary route/OD for 7 days)	Inhibited bacterial growth by increased phagocytic activity and phagocytic index. Enhanced lysosomal enzyme contents of the milk polymorphonuclear cells	Mukharjee et al. (2005)
		Wistar albino rats	Aqueous extract of <i>O. sanctum</i> leaf (100, 200 mg/kg/day/P.o. for 45 days)	Increased level of total protein, stimulated antibody production, enhanced production of WBC, RBC, and Hb Decreased SGPT	Jeba et al. (2011)
		Swiss albino mice	Ethanollic and aqueous extracts of <i>O. basilicum</i> leaves (400 mg/kg/day/P.o.)	Increase in circulating antibody titer production, percentage neutrophil adhesion ($p < 0.01$) to nylon fibers, phagocytic activity, and primary and secondary hemagglutination antibody titer ($p < 0.01$) Potentiate delayed-type hypersensitivity reaction	Neelam and Nilofer (2010)
		In vitro study, Cell preparation from Sprague–Dawley male rat and suspended in RPMI 1640 medium	Methanolic extract of <i>O. basilicum</i> (250 μ g/ml) Aqueous extract of <i>O. basilicum</i> (250 μ g/ml)	Lymphoproliferation up to 80% lymphoproliferation up to 83%	Flores et al. (2008)
		Stress-induced anxiety and depression model of male albino rats	Aqueous extract of <i>Ocimum sanctum</i> (100 mg/kg)	Anxiolytic and antidepressant-like effect mediated through central monoaminergic neurotransmitter system	Tabassum et al. (2010)

Table 1 (continued)

Herb name	Traditional uses	Study/study model	Preparation (dose)	Results	References
<i>Haridra (Curcuma longa)</i>	(1) Used with cow's urine in eosinophilia. (2) with curry leaves in asthma. (3) Turmeric powder, honey, and bitter gourd leaves extract used for measles. (4) Turmeric powder, powdered black pepper with milk used for Malaria. (6) Honey and turmeric powder mixed with the juice of Indian gooseberry treats urine discharges	NP-OVA immunized C57BL female mice	Curcumin, extracted from <i>Curcuma longa</i> (200 µg/day/I.p.)	Increases humoral immunity by antibody production mediated by increased TFH cells in the draining lymph nodes. Production of high-affinity antibodies of the IgG1 and IgG2b isotypes	Kim et al. (2019)
		In vitro, RAW 264.7 cells derived from murine macrophages and clone-9 rat hepatocytes	Concentrations of 20% turmeric polysaccharides ukonan A, B, C, and D extracted with water (TurP)	Promotes cellular immune responses, and tissue repair (improves telomer function)	Pan et al. (2017)
		C57BL/6 mice infected with LP-BM5 murine leukemia virus (MuLV)	A mixture of <i>Curcuma longa</i> and sweet purple potato (CPM) (CPM low—2 g/kg Bw/P.o.) (CPM high—5 g/kg Bw/P.o.)	Increased expression of MHC class I and CD8(+) T helper cells, T cell proliferation, phagocytic activity and improved the imbalance of Th1/Th2 type cytokines	Park et al. (2018)
		Swiss albino male mice	Nanoparticulate curcumin (doses of 5 mg/kg/day, 10 mg/kg/day/P.o.)	Stimulated primary humoral immunity with 9.00 ± 1.00 antibody titer ($p < 0.05$) white blood cells increased and the weight of the lymphoid organs was also increased	Afolayan et al. (2018)
		Pacific white shrimp (<i>Litopenaeus vannamei</i> Boone) against <i>V.harveyi</i>	<i>Curcuma longa</i> Linn. extract containing 25.726% (w/w) curcuminoids (0.12.5, 25.0 and 50.0 mg/kg feed)	Better resistance against <i>V. harveyi</i> in shrimps. Enhanced phenoloxidase activity and phagocytic activity	Kitima et al. (2010)
		Splenocyte culture made from swiss albino male mice	NR-INF-02 (an aqueous-based extract of <i>C. longa</i>) ((0.8–500 µg/mL)	Immunostimulatory activity by macrophage activation, splenocytes proliferation, and cytokine release down-regulating PGE2 and IL-12 secretion	Chandrasekaran et al. (2013)
		C57BL/6J—Min/+(Min/+) mice	A diet containing 0.1% curcumin	Increased mucosal CD4(+) T cells and B cells	

Table 1 (continued)

Herb name	Traditional uses	Study/study model	Preparation (dose)	Results	References
<i>Tvaka</i> (genous Cinnamomum)	(1) In Ayurveda, used for the common cold, cough, fever, sore throat, sinusitis, and herbal toothpaste to reduce dental caries. (2) In traditional Chinese medicine (TCM), used for cold, diarrhea, asthma and as an appetiser. (3) In Europe, used for ailments associated with cold. (6) In western herbal medicine, used in toothpaste because of its antimicrobial property	In vivo study, Nile tilapia, <i>Oreochromis niloticus</i> (L.). Fish challenged against hypoxia stress or pathogenic bacteria In vitro, Peripheral blood lymphocyte (PBL) culture	0.0, 0.25, 0.5, 1.0, 3.0, 5.0, and 10.0 g cinnamon nanoparticles (CNP)/kg/P.o 0.01% extract of Chinese medicinal herbs (CMH) containing Cinnamomum cassia (at the dilution of 40*)	Raised Innate immunity variables (nitrous oxide, nitro blue tetrazolium) and lysozyme activity were higher. No mortality in fish fed 3.0–10.0 g CNP/kg diet Stimulated human lymphocytes to proliferate	Abdel-Tawwab et al. (2018) Shan et al. (1999)

Table 1 (continued)

Herb name	Traditional uses	Study/study model	Preparation (dose)	Results	References
<i>Maricha (Piper nigrum)</i>	(1) In Ayurveda, used to treat respiratory congestion. (2) Used in cold and flu prevention in western herbalism. (3) Used in ear–nose–throat-related problems, including a cough, sinusitis, throat pain, throat infection, and earache. (4) Used against skin diseases, fever, and jaundice	<i>L. donovani</i> infected BALB/c mice	<i>Piper nigrum</i> hexane (PNH) (100 mg/kg, 200 mg/kg/I.P. and <i>P. nigrum</i> ethanolic (PNE) (100 mg/kg, 200 mg/kg/I.p.)	Increased secretion of Th1 (INF- γ , TNF α , and IL-2) cytokines and Decreased IL-4 and IL-10, Increased production of IgG2a, Upregulated expression of co-stimulatory molecules CD80 and CD86, Augmented splenic CD4 + and CD8 + T cell population, Induced strong lymphoproliferative and DTH responses and partially stimulated NO production	Chouhan et al. (2015)
		In vitro, murine cultured splenocytes	Aqueous extracts of black pepper or cardamom four doses (1, 10, 50, and 100 μ g/mL)	All doses (except 1 μ g/mL) enhanced splenocyte proliferation A dose-dependent increase in INF- γ release, IL-6 and TNF α release by macrophages	Maurya et al. (2020)
		BALB/c mice	AC II, a registered Ayurvedic preparation (1 g/kg BW/P.o.)	The enhanced mitogen-induced proliferation of spleen cell lymphocytes Enhanced NK cell activity in normal and tumor-bearing animals, Elevated levels of IL-2, TNF- α , and INF- γ in normal mice, Antibody-dependent cellular cytotoxicity was raised	Kesavan et al. (1998)

Table 1 (continued)

Herb name	Traditional uses	Study/study model	Preparation (dose)	Results	References
<i>Shunthi</i> (Dry <i>Zingiber officinale</i>)	(1) Ginger given orally for the common cold in India. (2) Ginger and palm tree juice (htan-nyat) are boiled and given orally to prevent the flu in Burma. (3) In China, sliced cooked ginger with brown sugar is used in the common cold. Dried ginger candies are used for coughing	Rainbow trout fish (<i>Oncorhynchus mykiss</i>) BALB/c mice	Diet (1% of a dried aqueous ginger extract) used at a rate of 2% of body wt. for 3 weeks 50% ethanolic ginger extract (25 mg/kg/P.o.)	Increased Non-specific immunity Phagocytosis and extracellular burst activity of blood leukocytes were higher Improved humoral immunity (higher antibodies and plaque-forming cells)	Dugenci et al. (2003) Puri et al. (2000)
<i>Chyawanprash</i>	(1) In Ayurveda, It is <i>Rasayana</i> (rejuvenating tonic) that helps in attaining longevity, memory, intellect, freedom from disease, youthfulness, luster, complexion, voice, and optimum strength of physique and sense organs	Cyclophosphamide immunosuppressed male swiss mice In vitro study done in dendritic cell (DC) and NK cell cultures from murine bone marrow Ovalbumin induced allergy in mice	Essential oil from <i>Zingiber officinale</i> (100, 200 and 400 mg/kg/OD/P.o. for 7 days) D-CHY (Dabar-Chyawanprash) (20–500 µg/ml for 24 h) D-CHY (1 g/kg/P.o.)	Recovered humoral immune response in immunosuppressed mice Discussed in manuscript Antiallergic activity by reducing plasma histamine levels and serum immunoglobulin E (IgE) release	Carrasco et al. (2009) Madaan et al. (2015) Sastry et al. (2014)

Table 1 (continued)

Herb name	Traditional uses	Study/study model	Preparation (dose)	Results	References
<i>Lavang (Syzigium aromaticum)</i>	(1) In tropical Asia, cloves are used to treat scabies, cholera, malaria, tuberculosis, diarrhea, and asthma. (3) It has been traditionally used in inhibiting food-borne pathogens in America	Albino Wistar rats Male Swiss mice	Flower bud oil of <i>Syzigium aromaticum</i> (200, 400, 800 mg/kg p.o.) Clove essential oil (CEO) (100, 200 and 400 mg/kg/P.o.) 400 mg/kg/P.o	Exhibited increase in haemagglutinating antibody titer and delayed-type hypersensitivity response in dose-dependent manner Increase in total WBC count and stimulating cell-mediated immunity in a dose-dependent manner Protective effect against immunosuppression	Umasankar and Nambikkairaj (2018) Carrasco et al. (2009)
		In vitro, macrophage cells isolated from BALB/c mice	Clove ethanolic extracted essential oil (containing eugenol) or aqueous extract (ranging from 0.001 to 1000 µg/ml)	Both extracts enhance NO release by non-LPS (unstimulated) treated macrophages at a concentration of (0.001–1 µg/ml) Ethanolic extract and aqueous extract (doses up to 1 µg/ml) showed suppression of TNF-α release while aqueous extract (doses > 1 µg/ml) showed stimulation of TNF-α release	
<i>Pudina (Mentha arvensis)</i>	(1) Used to treat cold, cough, fever, headache, and asthma. (2) Leaves have anti-inflammatory action. (3) A decoction is used to treat diarrhea and influenza	Sprague–Dawley rats	<i>Mentha arvensis</i> (MA) extract (100 mg/kg/P.o.) and fermented <i>Mentha arvensis</i> (FMA) (100 mg/kg/P.o.)	Pretreatment reduced the serum and hippocampus level of malondialdehyde (MDA) Ameliorated the serum and hippocampus nitric oxide (NO) levels in immobilized rats	Weishun et al. (2018)
<i>Ajwain (Trachyspermum ammi)</i>	(1) <i>Ajwain</i> seeds, clove, and common salt are used as lozenges for pharyngitis, sore throat, and hoarseness of voice. (2) Steam inhalation with <i>Ajwain</i> seed in common cold	Wistar rats In vitro, murine splenocyte cells	Crude methanolic extract of <i>T. ammi</i> (500 mg/kg/P.o.) <i>Ajowan</i> immunomodulatory component (ImC) (1 µg/ml)	Effective immunomodulation on skin thickness (DTH reaction) The induced proliferation of murine splenocytes activates peritoneal exudate cells for the synthesis of NO (nitric oxide) and phagocytosis	Siddiqui et al. (2019) Shruthi et al. (2017)

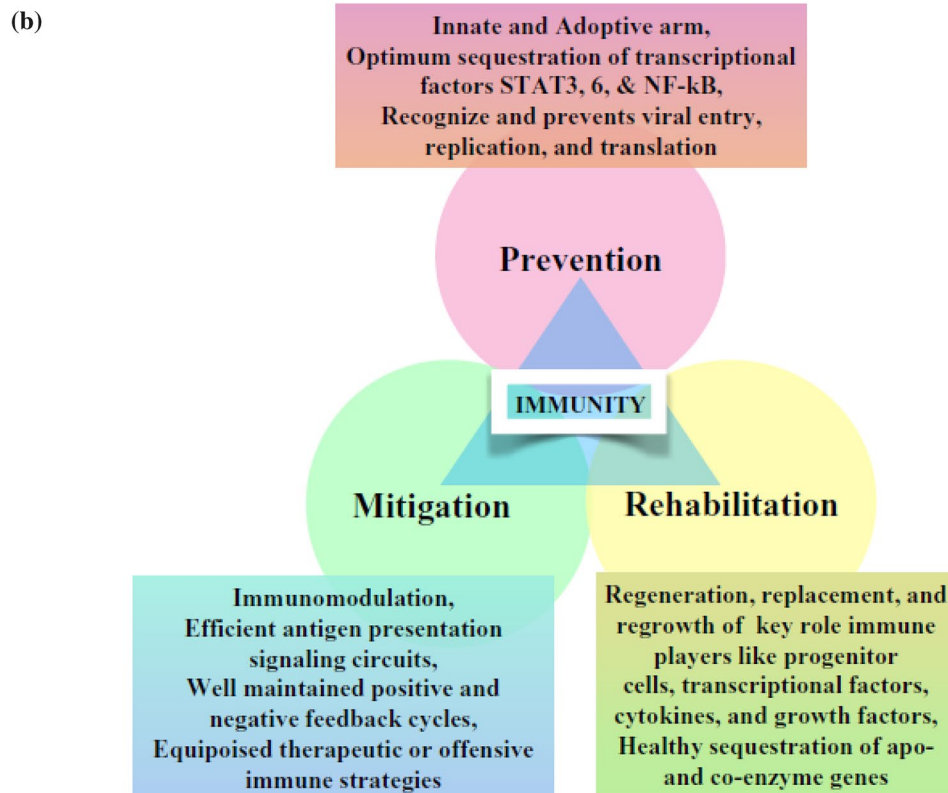
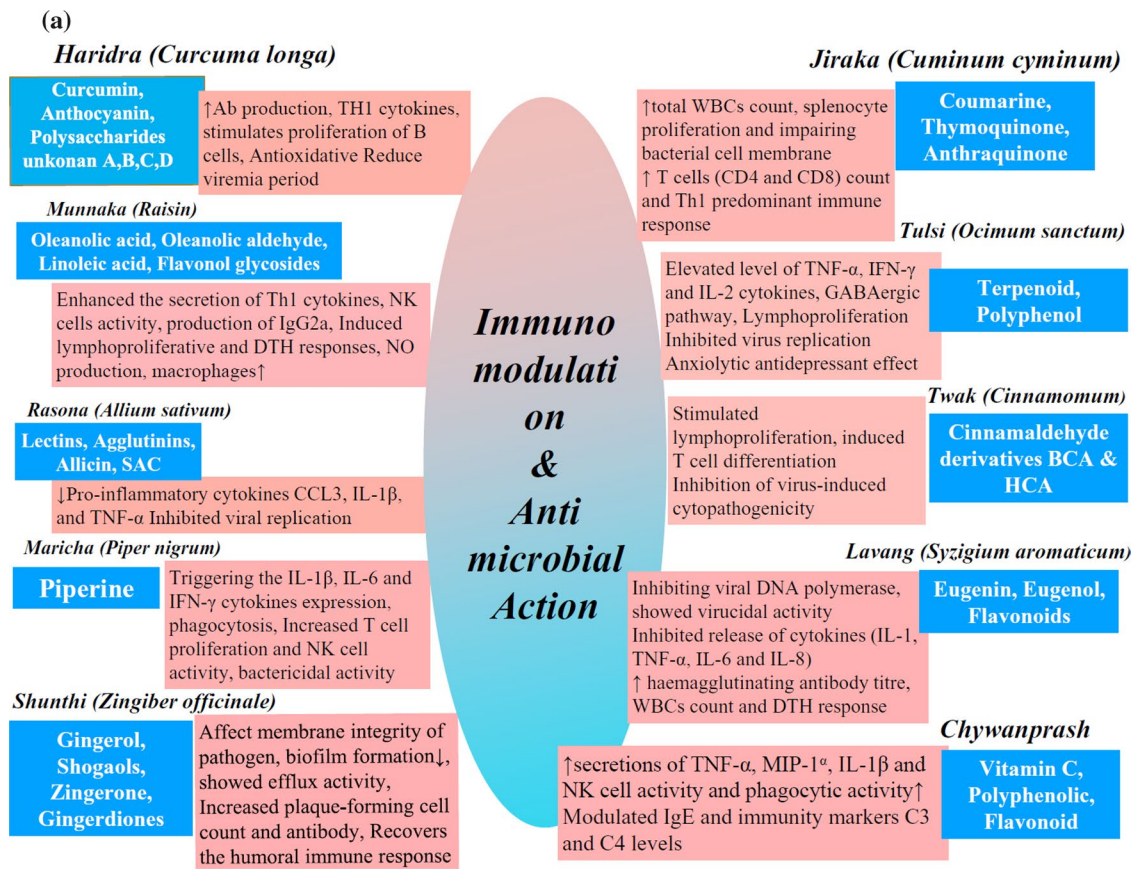


Fig. 1 a Immunomodulatory and anti-microbial action of herbs advised by AYUSH, India. Advised herbs, their major phytoconstituents, and possible mechanism of actions leading to immunomodulation, anti-microbial, and anti-oxidative actions. Ab—antibodies, Th1—T helper type 1, Nk cells—natural killer cells, IgG2a—immunoglobulin G 2a, DTH—delayed-type hypersensitivity, NO—nitric oxide, CCL3—Chemokines (C-C motif) ligand 3, IL-1 β —interleukin 1 β , IL-6—interleukin 6, IFN- γ —interferon-gamma, WBCs—white blood cells, CD4—Cluster of differentiation 4, TNF α —tumour necrotizing factor α , MIP 1 α —macrophage inflammatory protein α , and IgE—Immunoglobulin E. **b** Preventive, mitigation, and rehabilitation role of immunity to the viral threat

the immune cells as well as microbes that could also provide useful insights to the development of potentially useful new pharmacological agents (Fig. 2). **Rasona** is an Ayurvedic Sanskrit name for Garlic (*Allium sativum* L.; Family: *Amaryllidaceae*) that enhances the functioning of the immune system by stimulating macrophages, lymphocytes, natural killer (NK) cells, dendritic cells, and eosinophils, through mechanisms like modulation of cytokine secretion, immunoglobulin production, phagocytosis, and macrophage activation (Arreola et al. 2015). Garlic compounds, like sulfur-containing components, showed a modulatory effect on T cell proliferation. **Cuminum cyminum** (**Jiraka**) possesses immune stimulatory property possibly through thymoquinone (TQ). The black cumin seeds are proved effective for the treatment of diseases such as asthma, bronchitis, rheumatism, and other inflammatory diseases (Srinivasan 2018). *Cuminum cyminum* stimulated the T cells (CD4 and CD8) and Th1 cytokines expression in normal and immune-suppressed swiss albino mice (Chauhan et al. 2010). Antibacterial activities of cumin, cardamom, and dill weed essential oils were evaluated against *Campylobacter jejuni* and *Campylobacter coli* showed inhibition of *Campylobacter* species by impairing the bacterial cell membrane (Ingok and Guler 2017). *Coriandrum sativum* (*Dhaanyaka*) leaves contain vitamins, minerals (phosphorous, calcium and iron) and it is a major source of lipids, petroselinic acid, and monounsaturated fatty acid (Mandal and Mandal 2015). Plantaricin *C. sativum*, an antimicrobial peptide isolated from coriander leaf extract and coriander essential oil exhibited antimicrobial activities against different strains of bacteria's in two different studies (Masoud et al. 2014). Immunomodulatory and antimicrobial in vivo/in vitro and clinical studies of all recommended spices/herbs are summarised in Table 1.

An open level, comparative clinical study administering add-on Ayurvedic treatment with Standard of Care (SoC) in COVID-19 positive cases expressed fast recovery and early discharge in patients received *Dasamooladuthrayam Kashaya* and *Guduchi Kwatham* with SoC than SOC alone (Khedkar et al. 2020). Results of undergoing Ayurvedic herbs trials on recovery rate, virus loads, and

immunological markers of COVID-19 are awaited (Rangnekar et al. 2020).

Ayurvedic procedures

Ayurveda advocates *Nasya* (instillation of medicine through nostrils) for the prevention and mitigation of diseases. Absorption of drugs from the nasal cavity occurs through two routes i.e. paracellular (slow, passive, and aqueous route of transport) and transcellular (rate dependent, active and lipophilic route of transport) (Bale et al. 2015). Advisory recommended applying sesame oil/ coconut oil or *ghee* in both the nostrils twice daily (morning and evening) called *Pratimarsha nasya*. This therapy cleanses, purifies, and strengthens the nasal passages, likely to act as a “physiological mask” and may prevent virus fatty acid layer adherence to moist mucosa of the nasal or oral cavity (Tillu et al. 2020). The sesame seed oil contains important active compounds such as major lignans, phytosterols, and vitamin E especially γ -tocopherol which has immunomodulatory and antimicrobial activity (Nonaka et al. 1997). Advisory also recommended oil pulling therapy (*Kavala* or *Gandusha*: a traditional procedure in which the practitioner rinses or swishes oil in his mouth). It is supposed to cure oral and systemic diseases. It is a powerful detoxifying ayurvedic technique that is preventive as well as curative (Hooda et al. 2017). *Cocos nucifera* Linn. (Coconut) oil is an easily available edible oil that contains predominantly medium-chain fatty acids (lauric acid) that have proven anti-inflammatory and antimicrobial effects (Peedikayil et al. 2015). In an observer-masked, randomized, volunteer-based cross-over clinical trial, coconut oil pulling seems to have similar plaque inhibition activity as 2% chlorhexidine gluconate (CHX) with less tooth staining than CHX (Sezgin et al. 2019).

Non-pharmacological procedures like *Yogasan*, *Pranayama*, and *Dhyaan* (meditation) have been advised routinely at least 30 min/day in AYUSH guidelines to reduce stress, anxiety, enhance immunity, etc. Every day, an instructor displays the *Asanas* technique on the website of the AYUSH ministry in the form of a video for the people to follow. *Pranayama* (breath regulation) an essential component of *Yoga*, positively influences the physiology of the human body. Stress hurts the immune system and prolonged exposure is linked to physical and mental health problems (Segerstrom and Miller 2004). *Yoga* modulates levels of immunoglobulins and viral recognition cells (NK cells) and moderates C-reactive protein and other inflammatory cytokines in the blood (Shete et al. 2017). *Yoga* practice optimizes sympathetic responses of the body to stressful stimuli and restores autonomic regulatory reflex mechanisms by inhibition of the posterior or sympathetic area of the hypothalamus. It inhibits median forebrain centers and other areas liable for

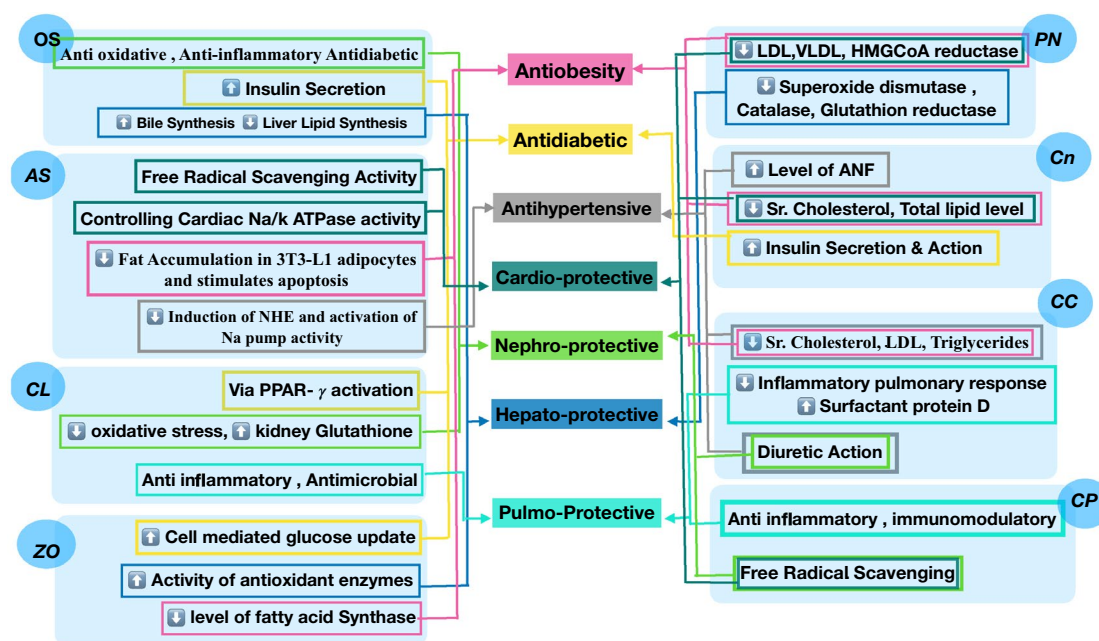


Fig. 2 Role of advised herbs in COVID-19 associated co-morbidities. Protective role of advised herbs and their mechanistic properties against co-morbidities associated with COVID 19. Mechanistic properties of herbs are reflected through the same colour lines, borders, and complete filled borders. Dual activity is shown in double colour boxes. OS: *Ocimum sanctum*, AS: *Allium sativum*, CL: *Curcuma*

longa, ZO: *Zingiber officinalis*; PN: *Piper nigrum*, Cn: *Cinnamomum*, CC: *Cuminum cyminum*, CP: *Chyavanprash*, Na/K-ATPase: Sodium potassium-ATPase, Ca: Calcium, PPAR- γ : Peroxisome proliferator-activated receptor-gamma, LDL: Low-density lipoproteins, VLDL: Very low-density lipoprotein, HMG-CoA: β -Hydroxy β -methylglutaryl-CoA, and ANF: Atrial natriuretic factor

fear, aggressiveness, and rage, coupled with stimulation of the rewarding pleasure centers resulting in a state of bliss and pleasure (Woodyard 2011) and increase multiple antidepressant neurotransmitters and hormones such as GABA, serotonin, dopamine (Stephens 2017) and decrease the levels of monoamine oxidase that breaks down neurotransmitters and cortisol (Kamble 2019). Yoga practices may inhibit the activity of the paraventricular nuclei of the hypothalamus, resulting in reduced ACTH production and decreased synthesis of cortisol, and aldosterone lead to down-regulate stress responses (Arora and Bhattacharjee 2008). The process and interrelation between stress, immunity, morbidity susceptibility, co-morbidities, and *Yogic* practices are summarised in Fig. 3.

Dhyaan (meditation) increases the expression of brain-derived neurotrophic factor (BDNF) and the thickness of the left hippocampus that essentially plays a role in the resiliency to chronic stress and depressive states (Taliaz et al. 2011). Chronic stress flare-up the aging process in association with decreased telomerase activity and telomere shortening. A big positive association between comprehensive lifestyle changes (including *Yoga*, meditation, breathing, healthy whole-food, and plant-based diet), and increased telomerase activity in human peripheral blood mononuclear cells was found (Ornish et al. 2008). An open-label

cohort study performed on 54 depression patients (high serum cortisol level), subjects in the *Yoga* groups (*Yoga* alone and *Yoga* with drug therapy) had significant drops in their cortisol levels in comparison to the drug-only group ($p < 0.008$). In *Yoga* only group, there was a high correlation between decreased cortisol levels and lower scores on the HDRS (Hamilton Depression Rating Scale) indicating a positive antidepressant effect as well ($p < 0.001$) (Thirthalli et al. 2013). A randomized controlled clinical test performed among high stressed college students assessed the consequences of sun salutations or *Suryanamaskar* (a series of 12 physical postures in conjunction with breathing). After 14 days of practice, the experimental group scored higher on mental calmness, joy, strength, physical relaxation and feeling at ease, and scored lower on physical fatigue, somatic stress, and negative emotional feelings in comparison with the control group (Godse et al. 2015).

Pranayama or breath regulation includes modulation of the pace of breathing, viz. slowing down or pacing the breath, manipulation of nostrils, chanting of humming sounds, retention of breath, etc. *Pranayama* techniques are also beneficial for treating a range of stress-related disorders. *Anuloma-Viloma-Pranayama* (AVP), i.e., alternate nasal breathing exercise creates negative pressure within the cavity hence improves oxygenation (better surface

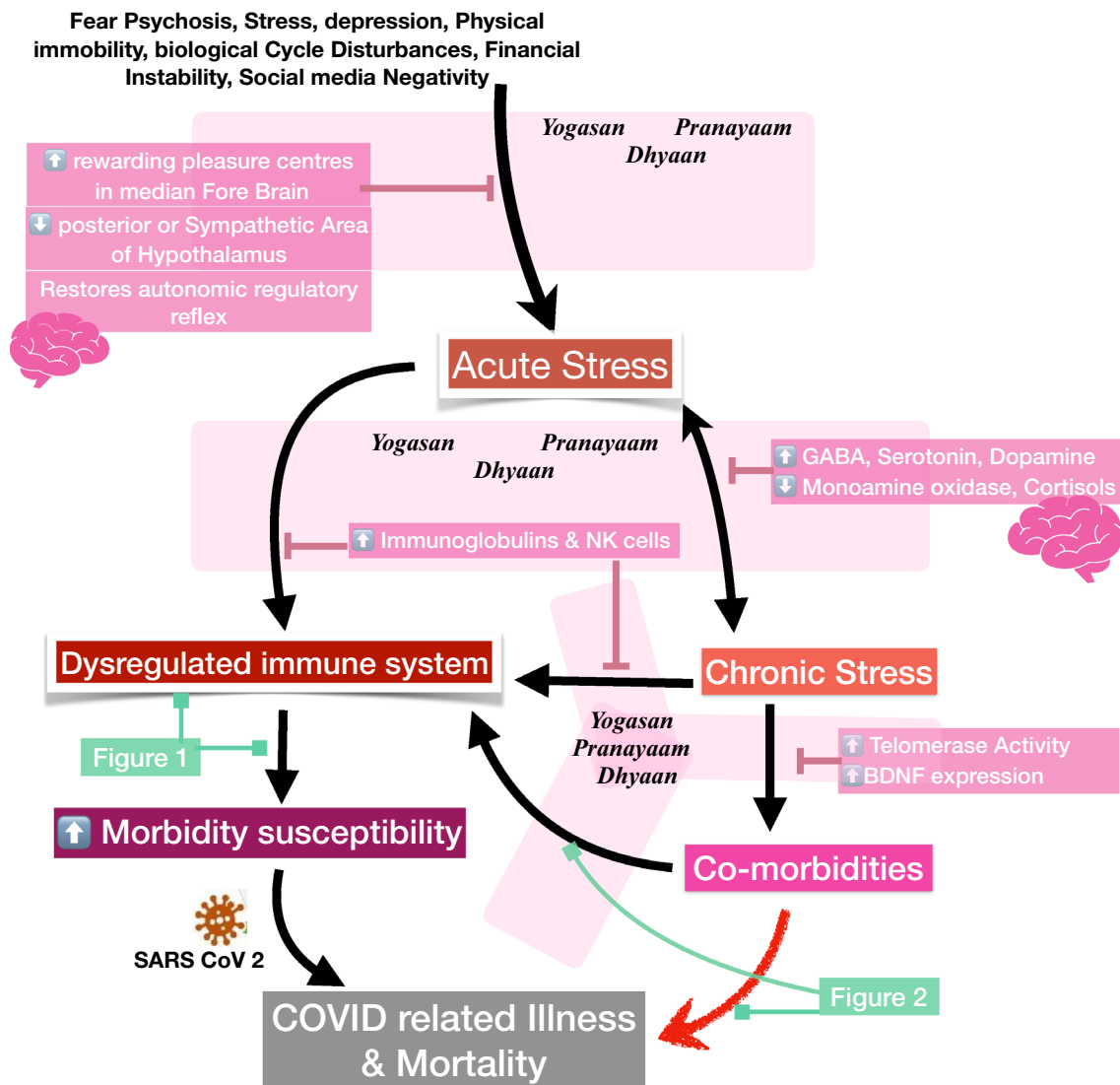


Fig. 3 Psychoneuroimmunology correlation and protective effect of *Yoga* in modulation of acute stress, chronic stress, equipose immune system, and COVID-19 associated co-morbidities. Multiple stimuli exaggerate acute stress leading to chronic stress and vice versa. Stress causing immune alteration eventually morbidity susceptibility and

prone to COVID-19 illness if contracted to SARS-CoV-2 virus. *Yoga* modulates, weakens, reduces the stress intensity through various mechanisms as shown in the figure. GABA—Gamma-aminobutyric acid, BDNF—Brain-derived neurotrophic factor, NK cells—Natural killer cells

availability) and ventilation of the paranasal sinuses and nasal respiratory epithelium (Bhardwaj et al. 2013). A set of 3 *Pranayama* breathing exercises was found to increase lung functions (PEF and FEV1) after only 6 weeks of three 10-min each practice sessions per week in healthy volunteers (Kupersmidt and Barnable 2019). The Intervention arm, COPD assessment test scores after 3 months of *Pranayama* practice, showed improvement in the subjective experience of health, disease severity, and functional status for COPD patients, with airflow limitation not fully reversible but usually progressive (Gupta et al. 2014). In an observational, prospective, quasi-experimental study done

on elderly COVID-19 patients (65 yrs or above) recruited from Hainan General Hospital and Huanggang central hospital, six-week respiratory rehabilitation improved respiratory function (FEV1, FVC, FEV1/FVC%, and DLCO%), Quality of life, anxiety and depression scores (Liu et al. 2020).

Yoga is effective in improving dyspnea, inflammatory markers, respiratory functions (Tidal volume, vital capacity, minute ventilation, respiratory rate, forced expiratory volume (FEV1) and forced vital capacity (FVC)), cardiac functions (blood pressure, heart rate, pulse duration, upstroke time, ejection duration index, diastolic time) and Quality of life as a standard cardiopulmonary rehabilitation

(Guleria et al. 2015). The *Yoga* practice induces beneficial changes in cardiovascular function in a parallel arm, open-label, single-blind, randomized controlled study conducted on elderly people (age above 60 yrs) with stage-I hypertension. The basal oxygen consumption is reported to be up to 15% less in regular yoga practitioners as compared to non-practitioner (Patil 2016). 3 months of regular yoga breathing practice is reported with decreasing oxygen consumption by 36% (Tyagi 2013). The effects of yoga on pulmonary volumes and respiratory muscle strength verified in 36 elderly women showed a decrease in heart rate (HR) and respiratory rate (RR) in the yoga group ($76-39 \pm 8-03$ vs. $74-61 \pm 10.26$ bpm and 18.61 ± 3.15 vs. 16.72 ± 3.12 res/min. respectively) with improved tidal volume, minute ventilation, vital capacity, maximal inspiratory pressure, and maximal expiratory pressure (Bezerra et al. 2014).

Ayurveda and *Yoga* can mitigate the health and social impact of COVID-19 illness. Ayurvedic pathophysiology of COVID-19 is understood (Pandkar and Sachdeva 2020) and multiple clinical results also support the standalone or adjuvant benefits of Ayurvedic medication. In a randomized placebo-controlled pilot clinical trial, Ayurvedic oil, herbs, and herbo-mineral preparations were administered orally and intranasal. Patients were evaluated for clinical severity, viral loads, and inflammatory markers. The study concluded that Ayurveda intervention can expedite viral dissemination, equiposed inflammatory markers, and no ADR link to intervention (Devapura et al. 2021).

Discussion

Ayurveda postulates a foremost treatment of any disease is *Nidan Parivarjan* (eradication of causative), followed by treatment of disease (*Sanshaman and Sanshodhan*) and followed by do's and don'ts related to illness, food, daily regimes, and seasonal regime (Prasad 2002). The two main factors that contribute to infection are exposure and poor immune status. In Ayurveda, the concept of *Vyadhi-kshamatwa* has many broad implications than the term "Immunity" used in modern medicine (Masram et al. 2014). The word *Vyadhi-kshamatwa* is made up of two words; *Vyadhi* (disease) and *Kshamatwa* (suppress or overcome). It is defined as *Vyadhibala-Virodhitwa* (antagonistic to the strength and virulence of the disease) and *Vyadhyutpada Pratibandhakatwa* (capacity to inhibit and bind the causes and factors of the disease). Acharya *Sushruta* has mentioned that the *Ojus* is the finest essence of all of our body tissue and this *Ojus* is said to be *Bala* (strength of body) (Trikam and Sharma 2002). There is a close relation between *Bala* and *Vyadhi-kshamatwa*, when there is an increase in *Bala*, there is an increase in *Vyadhi-kshamatwa* and vice-versa (Masram et al. 2014; Byadgi 2011). The continuous

accumulation of *Aama* (a pro-inflammatory product of impaired metabolic disorder) in the body blocks the channels of energy and nutrition, which in turn decreases the level of *Bala* and finally compromised the *Vyadhi-kshamatwa* of the body (Byadgi 2011). Stress, pathogens, viruses, various chemicals, wrong food habits, and so on are responsible for the accumulation of *Aama* in the body leading to increased susceptibility to disease. Drinking hot water is a basic measure to digest *Aama* (Tillu et al. 2020).

Ayurveda, the science of life, is based on preventive care employing *Dinacharya* (daily regime) and *Ritucharya* (seasonal regime) to maintain the balance of *Doshas* (maintain homeostasis of body and mind). Self-care advisory incorporates aspects of promotion and strengthening of *Vyadhi-kshamatwa* and *Bala*. Through centuries, India had managed/ combat pandemics (*Janpadodhwans*) through the wisdom of Ayurveda and natural resources (Priya and Sujatha 2020). Ayurveda literature promotes *Rasayana* therapy along with physical and social distancing from infected persons for prevention and overcomes epidemic situations (Rastogi et al. 2020). Traditional Chinese Medicine has applied its diagnostic concept in identifying the current syndrome (COVID-19) and treated accordingly. Ayurveda should also work on the same line of diagnosing through its diagnostic concepts following treatment according to *RogiBala* and *Vyadhi-kshamatwa*.

Immunity, immunomodulation, and SARS-CoV-2

The immune components have continuing inside-out and outside-in communication at molecular, cellular, histological, and systems levels to maintain the body homeostasis. This routine house-keeping vs. concerted strategized response to an incumbent situation (altered normal) dialogue is what keeps a human body healthy and able to overcome challenging situations. Host immunity against viral is largely innate (first and second lines of defense) and also auto-regulated. Acquired or memory-directed immunity usually does not need to kick in during a virus lytic cycle. When a virus changes from lytic to lysogenic cycle (i.e. assumes a more long-term association with the body), it leads to a powerful and unregulated innate immune response leading to devastating results.

For SARS-CoV-2, an unregulated cytokine storm seems to be an important watershed reaction leading to fatality. Just like in allergic response, some persons may and some may not respond to an allergen in the environment because of 'primed' dendritic and other antigen presentation cells that process and activate the allergenic circuit. Similarly, 80% of individual do not show symptoms of SARS-CoV-2 although they harbour the virus in their body and may act as carriers, while others (15%) show moderate symptoms, and only 5% show the severe form of disease requiring ventilation and

these individuals (with or without co-morbidity) tend to succumb to the COVID-19. SARS-COV-2 manifestation is akin to other influenza viruses such as HKU-1, NL6, and OC43 which cause mild forms of pneumonia. SARS-COV-2 on the other hand is unusual in the sense, it quickly unlocks its replicon and usurps the host's transcriptome using its enzymes 3CLpro, RDRP, and other NSPs. ACE-2 is expressed on all blood vessel cells, monocytes, dendritic cells, and macrophages in tissue spaces that interact with spike protein of virus for internalization inside the host cell. It resulted in inflammation (innate immune response), release low levels of IFN- γ , and then the mononuclear macrophages start secreting high levels of IL-6, TNF- α , IL-1b, etc. Soon potent inflammation-inducing cytokines secreted in large quantity relentlessly and lost regulatory mechanism to stop it. A positive feedback loop seems to be the hyper-response to the viral proteins that cannot be controlled. Under these circumstances, an efficient immune system needs to have the right proportion of all cells. The signal reception nodes of all the immune circuits must be in good functioning so that once they can respond, certain stimuli be intercepted, and once mounted it must not go on for a very long-time unabated unchecked. The other important thing is the rejuvenation (regeneration, replacement, and repair) of damaged and used-up components of the immune system. The preventive, mitigation, and rehabilitation role of immunity to viral threat is shown in Fig. 1b. AYUSH advisory's phytochemicals and *Yoga* may induce the Th1/Th17 response for macrophage activation and elimination of SARS-COV-2 pathogens. They could support regenerating the required repertoire for the development of certain cell types to be efficiently and correctly occurring during infection (Rastogi et al. 2020; Kar et al. 2015; Das et al. 2016).

From data generated by scientific experiments, curcumin, piperine and various phenolic compounds (Paul et al. 2018; Das et al. 2015) have already shown immune-boosting not in the sense of activation but rather to maintain, regenerate, and ensure the efficiency of key immune components and their connecting circuitry in the rest of the systems (none of them exist in isolation). Nutritional ligands of PPAR- γ like *Curcuma Longa* and others are under scrutiny as a potential candidate for cytokine storm modulation in COVID-19 (Ciavarella et al. 2020). Pro-inflammatory innate responses are not misfired and in case there is an over-stimulation, they act as inflammation regulatory elements to bring the inflammatory cascade down. Almost 10 herbal drugs are screened for their immunomodulation effects (Fig. 1a). Recently, a clinical trial of some Ayurveda drugs as add-on therapy and standard care for COVID-19 has been launched. The lead herbs are *G. glabra* Linn., *W. somnifera* Linn., *T. cardifolia*, *P. longum* and poly-herbal medicine. *Chyawanprash*, a component of advisory contains these four herbs;

hence *Chyawanprash* could also be extended to COVID-19 care if trials post positive results.

Suffice it to say, the functional food, prophylactic-therapeutic phytochemicals, Ayurvedic procedures, frequency and synchronicity of important diurnal events for maximum efficacy by the chrono-biological system of the body's cells and their bioavailability to affected tissue, may ensure transcriptomic and/or metabolomic sequestration of the required components (cellular and non-cellular) and their proper communication in the body with time to ensure optimum balance to keep the immunity (*Vyadhukshamata*), *samprapti-vigathan* (break of disease cascade), etc. in synchrony. Self-care advisory can streamline and maintain immunological, social, diurnal, and mental balance. Ayurveda fortified by *Yoga*, *Dhyana*, and *Pranayaam* ensure perfect rhythm and well-stocked repertoire of an already efficient and well-endowed immune system to combat the current pandemic situation.

Apprehensions about AYUSH advisory

Evidence, drug interaction, efficacy, and safety

An international advisory released by WHO, welcoming innovation like drug repurposing and traditional medicine in search of a potential treatment for COVID-19. This advisory also expressed concern for safety, efficacy and adverse side effects of certain remedies like *Artemisia annua* Linn. (family—Asteraceae) (Sweet wormwood, Chinese name-qinghao and famous as COVID-ORGANICS) touted as possible treatment backed by several African nations. “**Natural and safe**” a perception linked with herbal products is not always true. Many herbs have reported toxicity and adverse drug reactions. Clinical, in vivo and in vitro safety and toxicity profile studies for advised drugs are searched, analyzed, and discussed in Table 2, Although most of these herbs are food or dietary supplements so pharmacological vigilance is not compulsory. Sufficient works had been carried out on *Chyawanprash*, no evident information on toxicity has been available to date. It is considered safe in prescribed dosage (10 g/P.o. in the morning as recommended by AYUSH advisory). Agbaje et al. (2009), concluded that indiscriminate and long-term use of *Syzigium aromaticum* could be hazardous to body health so must be ingested with caution. (already in below table). No study has shown any significant toxicity except few in doses much higher than therapeutic limits. We searched *Uppsala Monitoring Centre* (UMC) (www.vigibase.org) and *Ayushsuraksha* (AYUSH pharmacovigilance reporting site) (www.ayushsuraksha.com) for adverse drug reactions (ADRs) associated with these herbs. UMC on date 23th May 2020, ADRs reported for *P. nigrum*, *O. sanctum*, *C. cyminum*, *Cinnamomum*, and *M. arvensis* are 2, 1, 6, 68, and 26 respectively. ADRs for *A. sativum*, *Z. officinalis* and

Table 2 Toxicological studies of Indian AYUSH advised herbs

Herb name	Study	Preparation	Study model	Dose/route	Results	References
<i>Allium sativum</i>	Sub-chronic toxicity study (90 days)	Methyl propyl trisulfide	Sprague–Dawley rats	0, 0.5, 2, and 6 mg/kg/day/P.o	No adverse effects in clinical observations, hematological findings, clinical bio-chemistry parameters, and histopathological examinations	Bastaki et al. (2018)
<i>Cuminum cyminum</i>	Sub-chronic toxicity study (45 days)	Essential oil	Healthy female wistar rats	0, 250, 500, and 1000 mg/kg/day/P.o	No adverse effects on clinical signs, body weight, hematological, biochemical parameters, and organ histology. No mortality	Taghizadeh et al. (2017)
				1000 mg/kg/day/P.o	Increased serum alanine transaminase (ALT) level	
<i>Coriandrum sativum</i>	Acute toxicity study	Seeds extract	Female swiss albino mice	1000, 3000 and 5000 mg/kg/OD/P.o	No behavioral changes and no mortality	Patel et al. (2012)
	Sub-chronic toxicity study	Seeds extract	Female swiss albino mice	1000 mg/kg/P.o	No alterations in hematological profile, histology, relative organ weights, and plasma markers of vital organs tissue damage	
				2000 and 3000 mg/kg/P.o	Significant reduction in food intake, body weight, and plasma lipid profiles	

Table 2 (continued)

Herb name	Study	Preparation	Study model	Dose/route	Results	References
<i>Ocimum basilicum</i> / <i>Ocimum sanctum</i>	Acute toxicity test	50% ethanolic leaf extract of <i>O. Sanctum</i>	Swiss albino mice	200, 600, & 2000 mg/kg/P.o	No hazardous symptoms like Central nervous system and Autonomic nervous system toxicities or death	Gautam and Goel (2014)
	Sub-chronic toxicity study (45 days)	Hydroalcoholic leaves extract of <i>O. basilicum</i>	Wistar rats	500 mg/kg/day/P.o	Reduced hematocrit, platelets, and RBC count	
				50, 500, 1000 & 2000 mg/kg/day/P.o	Neither deaths nor adverse effects were seen on serum parameters (glucose, creatinine, albumin, cholesterol, LDL, HDL, VLDL, SGPT, SGOT)	
<i>Curcuma longa</i>	Acute toxicity study	The essential oil of <i>O. basilicum</i>	Wistar albino rats	5–1000 mg/kg/P.o gavage	No abnormalities on day 1	Krishnaraju et al. (2009)
				1500 mg/kg/P.o gavage	Brief torpor just after gavages disappeared after few minutes	
				2000 and 3000 mg/kg/P.o gavage	Stayed torpid throughout the day with no mortality	
Cinnamon species	Sub-chronic toxicity study	Demethylated curcuminoids	Sprague–Dawley rats	3500 mg/kg/P.o, gavage	Mortality 100%	Ahmad et al. (2015)
				5000 mg/kg/P.o	No mortality and no signs of toxicity during the observation (14 days) and thereafter	
					No adverse effects and no evidence of genotoxicity	
	Sub-chronic toxicity study (90 days)	Turnipure Gold (extract formulation)	Sprague–Dawley rats of either sex	500, 1500, and 3000 mg/kg/P.o	No adverse effects on behavior, water intake, food consumption, hematological parameters, and mortality	Ahmad et al. (2015)
	Sub-acute toxicity study	Aqueous extract	Female Sprague–Dawley rats	0.1 g/kg/P.o		
				0.5 and 2 g/kg/P.o	A slight decrease in weight of kidney and liver	

Table 2 (continued)

Herb name	Study	Preparation	Study model	Dose/route	Results	References
<i>Piper nigrum</i>	Acute toxicity study	Aqueous extract	Sprague–Dawley rats of either sex	5000 mg/kg/P.o./OD	No signs of toxicity. No behavioral changes, No mortality, No histopathological changes in selected internal organs	Siharat et al. (2007)
	Sub-chronic toxicology study (90 days)	Aqueous extract	Sprague–Dawley rats	300, 600 and 1200 mg/kg/P.o	No abnormalities in body weight, hematological parameters, biochemical parameters, and histopathology	
<i>Zingiber officinale</i>	Sub-chronic toxicity study (45 days)	Ginger powder	Sprague–Dawley rats	500 mg/kg/P.o	No abnormalities in general conditions, behavior, growth, food and water consumption and hematological parameters, No mortality	Rong et al. (2009)
				1000 and 2000 mg/kg/P.o	No changes in biochemical parameters except a dose-dependent decrease in serum lactate dehydrogenase	
	Sub-chronic toxicity study (13 weeks)	Ginger oil	Wistar rats	2000 mg/kg/P.o 100, 250, and 500 mg/kg/day/P.o	Reduced weight of testes No mortality No adverse effects on body weight, organ weights, food consumption, hematological parameters, biochemical parameters, and histopathology of selected organs	
Raisin (dried grapes)	Sub-chronic toxicity study (90 days)	Grape seed extract with less than 5% catechin monomers	Sprague–Dawley rats	0, 0.5, 1.0, or 2.0% of diet	No toxicologically significant changes in clinical signs, hematological parameters, ophthalmology evaluations, and histopathological findings	Wren et al. (2002)
	Acute toxicity study	Proanthocyanidin-rich extract from grape seeds	Fischer 344 rats	2 and 4 g/kg/P.o	No evidence of acute oral toxicity	

Table 2 (continued)

Herb name	Study	Preparation	Study model	Dose/route	Results	References
<i>Syzigium aromaticum</i>	Acute toxicity study	Aqueous extract	Healthy Swiss albino mice and Wistar rats of both sexes	500–5000 mg/kg/P.o	No physical changes in the skin, fur, eyes, respiratory system. No change in behavioral pattern. Abdominal writhing was found, few animals died before the end of the study. LD50 was 2500 mg/kg/P.o	Agbaje et al. (2009)
	Sub-chronic toxicity study (90 days)	Aqueous extract	Swiss albino mice and wistar rats	300 and 700 mg/kg/P.o	Shown effects on hematological parameters Altered (decreased) serum electrolytes and increased serum urea. Severe and irreversible histological changes in brain, kidney, liver, stomach	
<i>Mentha arvensis</i>	Subchronic toxicity study (for 20, 40, and 60 days)	Petroleum ether extract of the leaves	Male albino mice	10 and 20 mg/mouse/day/P.o	Dose and duration-dependent reduction in the number of offspring of treated male mice mated with normal females. Reversible fall in weight of testis, epididymis, and sperm count. No alterations of serum protein, bilirubin, SGOT, SGPT, acid phosphatase, blood urea, and hematological indices	Sharma and Jacob (2001)
<i>Trachyspermum ammi</i>	Acute toxicity study	Methanolic seed extract	Wistar rats	400, 800, 1600, and 3200 mg/kg/P.o 1600 mg/kg/P.o 800 mg/kg/P.o 400 mg/kg/P.o	Two deaths occurred after 24 h in rats administering crude extract up to 3200 mg/kg/P.o Skin allergy, difficulty in breathing, and convulsions Fewer side effects than the higher dose No side effects	Siddiqui et al. (2019)

C. longa are 216, 399, and 226 respectively while *Chyawanprash*, *S. aromaticum*, and *T. ammi* has no reported ADR to date. These numbers are negligible in comparison to ADRs reported of another prophylactic drug like hydroxychloroquine (23,994) and paracetamol (149,820). The above data support the safety of advisory for longer human uses. Although limited access and information are available may be due to under-reporting or less known reporting procedure. *Ayursuraksha*, an Indian ASU pharmacovigilance reporting site, has no available data for public access to get an idea of ADRs reported to date for a particular herb, active ingredient, and their combination.

Guidelines issued are self-care, so no unsubstantial claims and no Ayurveda professional practice is promoted. Ministry of AYUSH issued a notification prohibiting the mongering of unsubstantiated and unauthenticated claims of curing COVID-19 through AYUSH medicines. It stated that all Indian states and Union Territories are directed to stop or prevent publicity and advertisement of AYUSH related claims for COVID-19 treatment in television, print media, and electronic media. This step has fairly regulated the claims made through e-platforms and print media (Anonymous 2020).

International relevance

More than 30 traditional medicine guidelines (for treatment alone 26 from china, 2 from South Korea) for prevention, prophylaxis, and treatment of COVID-19 have been issued till 12 May 2020. Many nations have adopted the translated version like Japan has adopted the translated version of Traditional Chinese Medicine (Lin et al. 2020). Indian AYUSH self-care guideline is translated in 5 united nation (UN) languages and 3 other international languages; hence it was eminent to see such advisory in light of current science and public health prospect.

Stress, anxiety, depression, fear, psychosis, psychoneuroimmunological correlations, and Yoga

The concept of the psychosomatic phenomenon has its roots in one of the traditional/classical *Yoga* texts (The *Yoga Vashista*, codified nearly 5000 years ago) termed as *Adhija-Vyadhi*. Uncontrolled, long-standing stress at *Manomaya Kosha* (Mental body) may lead to disturbances in the *Prana* (vital energy—similar to Qi), and manifest the disturbances in the *Annamaya Kosa* (Physical body) may result in several psychosomatic diseases. Stress, anxiety, depression, fear psychosis, sleep disturbances, loneliness (lockdown effect) are associated with the ongoing COVID-19 pandemic. Psychoneuroimmunology (PNI) studies showed correlation between the state of mind and the state of physical health (Singh et al.

2015). Eustress helps to cope with the demanding situation at the physical, mental or emotional level, but uncontrolled long-standing stress/chronic stress can have an immunosuppressive effect, a risk factor for COVID-19. Stress may dysregulate different immune parameters (e.g. inflammatory pathways) and lead to disease. Elevated pro-inflammatory cytokine production may generate sustained upper respiratory infection symptoms. Limited studies are carried out to evaluate the effect of *Yoga* on the immune system and it may decrease IL-1 β , IL-6, and TNF- α in inflammatory stages and reflects immunomodulation (Falkenberg et al. 2018). Increasing psychological resources (mindfulness, body consciousness, self-transcendence, spiritual peace, and social connectedness) may bring about salutary effects on emotional wellbeing. PNI correlation and protective effect of *Yoga* in modulation of acute stress, chronic stress, comorbidity, and immune system are explained in Fig. 3.

Endocrine, nervous and immune systems are interconnected, so disruption in one creates an impact on the other. *Yoga* activates neurohormonal mechanisms by inhibiting the posterior or sympathetic area of the hypothalamus, optimizes sympathetic responses to stressful stimuli, restores autonomic reflexes associated with stress, increases the parasympathetic activity thus reduces stress, anxiety, balances autonomic functions and hormonal secretions (Balasubramaniam et al. 2013). *Yoga* therapy was also found beneficial in enhancing immunity, sleep, cardio-pulmonary fitness, and telomere length in regular practitioners (Ornish et al. 2008; McCall et al. 2013). The above discussion supports that *Yoga*, *Pranayam*, and *Dhyaan* can be a better way of managing stress in the current pandemic situation.

Co-morbidities management through drugs and non-pharmacological procedures

Emerging data suggest an increased association and a heightened mortality in patients of COVID-19 with co-morbidities (Singh et al. 2020). Co-morbidities predispose the patients to multi-organ failure during an infection. According to a recently published study on laboratory-confirmed cases of COVID-19, patients with any comorbidity yielded poorer clinical outcomes than those without. A systematic review and meta-analysis on the prevalence of co-morbidities and their effects in COVID-19 patients revealed that underlying disease, including hypertension, respiratory system disease, and cardiovascular disease, may be risk factors for severe patients compared with non-severe patients (Yang and Zhou 2020). Hence advised drugs were screened for various morbidities associated with COVID-19. It was observed that all herbs protect from single or multiple co-morbidities collectively or individually. The role of advised herbs and their mechanism of action against co-morbidities associated with COVID-19 is explained in

Table 3 The activity and mechanistic properties of the herbs advised by Indian AYUSH for COVID-19

Activity	Herb	Mechanistic property
Anti-obesity	<i>Allium sativum</i>	Decreased fat accumulation in 3T3-L1 adipocytes and stimulates apoptosis
	<i>Zingiber officinalis</i>	Decreases the level of fatty acid synthase
	<i>Piper nigrum</i>	Reduces LDL, VLDL, HMGCoA reductase
	<i>Cinnamomum</i>	Reduces Serum cholesterol
	<i>Cuminum cyminum</i>	Reduces Serum cholesterol, LDL, and triglycerides
Anti-diabetic	<i>Ocimum sanctum</i>	Enhances Insulin secretions
	<i>Curcuma longa</i>	Act through PPAR-activation
	<i>Zingiber officinalis</i>	Increases cell-mediated glucose uptake
	<i>Cinnamomum</i>	Enhances Insulin secretions and their action
Antihypertensive	<i>Allium sativum</i>	Reduces induction of NHE and activation of Na pump activity
	<i>Cinnamomum</i>	Increases level of ANF
	<i>Cuminum cyminum</i>	Reduces Sr. Cholesterol, LDL, triglycerides, act as a diuretic
Cardioprotective	<i>Allium sativum</i>	Free radical scavenger, Controls cardiac Na/K ATPase activity
	<i>Piper nigrum</i>	Reduces LDL, VLDL, HMGCoA reductase
	<i>Chywanprash</i>	Free radical scavenging
	<i>Cinnamomum</i>	Reduces Serum cholesterol, and total lipid level
Nephroprotective	<i>Ocimum sanctum</i>	Anti oxidative and free radical scavenging
	<i>Curcuma longa</i>	Reduces oxidative stress and increases kidney glutathione content
	<i>Cuminum cyminum</i>	Diuretic action
	<i>Chywanprash</i>	Free radical scavenging
Hepato-protective	<i>Ocimum sanctum</i>	Increase bile synthesis, reduces liver lipid synthesis
	<i>Zingiber officinalis</i>	Anti-oxidant action
	<i>Piper nigrum</i>	Reduces superoxide dismutase, catalase, glutathione reductase
Pulmo-protective	<i>Curcuma longa</i>	Anti-inflammatory activity
	<i>Cuminum cyminum</i>	Manages inflammatory pulmonary response, increase activity of surfactant protein D
	<i>Chywanprash</i>	Settle pulmonary ailments, immunomodulatory

Fig. 2 and Table 3. Yoga has also gained popularity as an adjunct therapeutic tool in the management of diabetes, hypertension, obesity, respiratory disorders, autoimmune disorders and other psychosomatic illnesses (Ornish et al. 2008; McCall et al. 2013) hence may equally contribute to co-morbidities management.

Post-COVID-19 rehabilitations

Evidence from China has shown that recovery will be longer and more complex in COVID-19 patients due to neurological, cardiovascular, and respiratory after effects. The symptoms of COVID-19 disease can range from very mild to severe. Community-acquired pneumonia, ARDS, acute cardiac injury, stress, depression, and acute kidney injury in COVID-19 patients results in decreased activities of daily living and quality of life accompanied by decreased physical and mental function. Many research studies support that Yoga therapy is reported to relieve post-traumatic stress disorder symptoms in war veterans, tsunami survivors, hurricane refugees, and flood survivors (Tyagi 2013). Based on the above discussion, Yoga therapy may prove a beneficial

rehabilitative strategy in patients having a history of severe symptoms of COVID-19 in improving dyspnea, inflammatory markers, respiratory functions, cardiac functions, quality of life, and post-traumatic stress disorder as shown in Fig. 4. AYUSH guidelines can help to get back, improve the functioning system of the body as standard rehabilitation therapy (Fig. 5).

There is a need to document the feedbacks of self-care advisory and in this regard, the Indian AYUSH ministry's attempt of "Ayush Sanjeevani" mobile application (covered > 100 thousand downloads and > 1 million cumulative feedbacks as of 19 June 2020) and *Arogyaduta* are appreciable. Advisory has streamlined the AYUSH human resources (> 7 lakh AYUSH practitioners) and associated infrastructure (near 25,000 health facilities) in India.

Conclusion

From time to time, scientific advisory released by the national government of a country has great significance and is considered as an important medical guideline but

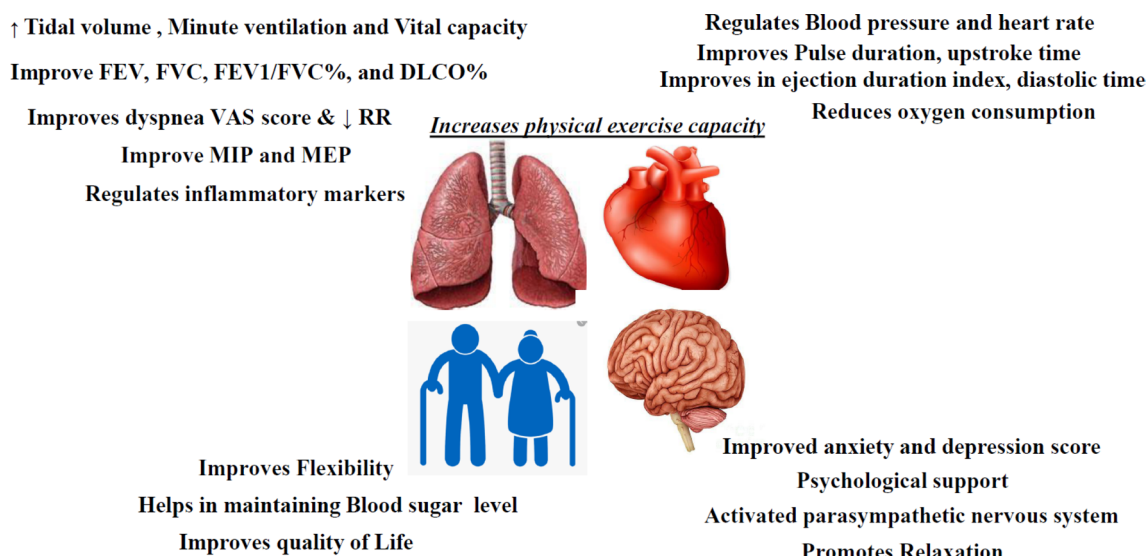
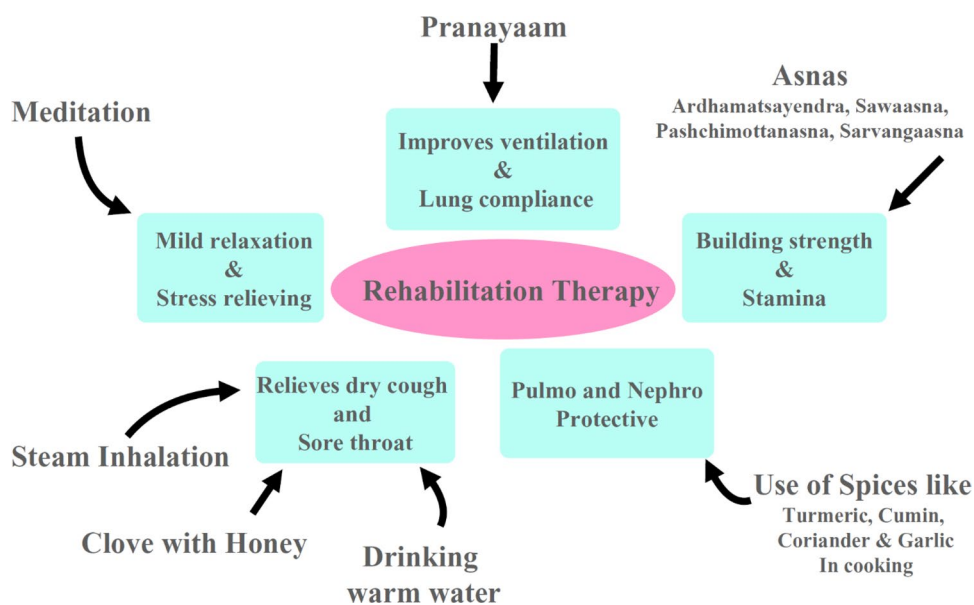


Fig. 4 Schematics representation of post-COVID-19 rehabilitation and *Yoga*. Figure shows post COVID-19 utility of *Yoga* in cardiopulmonary, mental, and co-morbidities rehabilitation

Fig. 5 AYUSH guideline can help to get back, keep, or improve the functioning system of the body as a standard rehabilitation therapy through routine procedures, meditation, *Pranayama*, herbs, and *Asanas*



the modern medical fraternities have some apprehension for the unconventional method like AYUSH. The information discussed in this article is the rationale behind advisory and will gradually increase the wisdom to provide an alternative to a large Indian community. The detailed immunological and other scenarios of herbal medicine are portrayed in Fig. 1a in terms of B-cell/T-cell response, cytokines release, and antimicrobial activity. It can be concluded that AYUSH-advised herbs and *Yoga* promote the state of immunity preparedness to threat, and equipose the immunity in COVID-19, COVID-19 related co-morbidities (Fig. 2) and stress management. It may be a simple,

safe, cost-effective, accessible, acceptable, infrastructure compatible, pragmatic for a longer duration, and sustainable preventive and prophylaxis approach for COVID-19. AYUSH ministry advisory not only supports the health of COVID-19 people but also creating a mental state that one can remain safe following home remedies (Rajkumar 2020). It is adoptive in nature and in the long run, it will change an individual's habits that may reduce the burden of overall health care. It was an advisory release for pan India which may have a pan globe following. We have thoroughly searched the scientific domain for each component of advisory for its pharmacological relevance. We conclude

that this advisory comes up with a strong scientific rationale and further indicated more precise research in clinical/observational trials concerning COVID-19 and prevention of other infections. This advisory can pave the way to overcome this pandemic and may open a new window for the effective use of traditional medicines throughout the world. Considering the properties of flora, *Yoga*, and procedures, this advisory encouraging us to get closer to the natural way of healing.

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Declarations

Ethical Statement This article does not contain any studies involving animals performed by any of the authors. This article does not contain any studies involving human participants performed by any of the authors.

Conflict of interest Prashant Kumar Gupta, Kishor Sonewane, Mariappan Rajan, Nitin J Patil, Trapti Agrawal, Ena Ray Banerjee, Nagendra Singh Chauhan, Awanish Kumar declare that they have no conflict of interest.

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