Review Article

A Review on Ayurvedic Medicinal Herbs as Remedial Perspective for COVID-19.

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ABSTRACT

Introduction: Recent outbreaks in a new type of coronavirus, novel coronavirus (COVID-19) disease causing respiratory infection have significantly hampered the public health. Traditional herbs provide enormous scope to bring out viable alternatives against viral diseases, considering non-availability of suitable drug for emerging viral diseases. The present review on plants and related phytochemicals will provide a viable options for controlling viral diseases particularly COVID-19 by maintain the immune system in current pandemic.

Methods: The methodological activities involved during a literature review were; (1) designing the review concept, (2) conducting the review on review papers, research papers, bulletins, official websites, (3) analysis of previous publications and (4) writing up the review paper. Major well-known bibliometric information sources studied are the Web of Science, Scopus, Mendeley and Google Scholar. Several keywords like name of plants, immunomodulatory, antiviral, coronavirus, COVID-19, Ayurvedic herbs, traditional medicine were chosen to obtain a large range of papers to be analyzed. The integrative literature review and paper preparation process was done from our own practical experience and influenced by various guidelines during February 2020 to May 2020.

Results: Herbal medicines and their active phytochemicals against some viruses including severe acute respiratory syndrome (SARS), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes COVID-19 pandemic, middle east respiratory syndrome coronavirus (MERS-COV), rhinovirus, human herpes virus (HSV-I & II), human immunodeficiency virus (HIV), coxsackievirus (CV), enterovirus 71 (EV71), hepatitis B virus (HBV), hepatitis C virus (HCV), herpes simplex virus, influenza A/H1N1 virus, coronavirus and respiratory syncytial virus (RSV) were extensively reviewed. In view of the possible benefit of herbal medicine for the prevention and control of the viral infectious diseases, Ayurvedic herbs could be useful an alternative and integrated approach to decrease the morbidity and mortality and enhance host immunity against COVID-19 attack.

Conclusion: Ayurvedic herbs have enough possibilities to be employed both for the prevention and treatment of COVID-19. The traditional practices and scientific evidences of such herbs and their phytochemicals against lethal viral infections *in-vivo* and *in-vitro* studies could be useful for a novel source of natural product in particular focus on COVID-19.

Key words: Ayurvedic Medicine, Antiviral herbs, Phytochemicals, Immunity boosting, SARS-CoV-2.

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INTRODUCTION

Medicinal plants used in traditional practices provide enormous scope to bring out viable alternatives against viral diseases, considering non-availability of suitable drug candidates and increasing resistance to existing drug molecules for many emerging and re-emerging viral diseases [1]. Herbal medicines and purified natural products provide a resource for novel antiviral drug development and immunomodulatory herbal remedies [2]. From 1940 to 2014, 49% of all small molecules approved by the US Food and Drug Administration were natural products directly linked to them[3]. Phytoconstituents and herbal remedies are being used against coronavirus studies with the expectation to support immune system and rest the body foundation. However further studies are needed for these new compounds to be up to modern pharmacological standards[4] . Methanolic extracts of 41 plant species used in the traditional medicine in Nepal were investigated for *in vitro* antiviral activity against viruses. The extracts of Nepalese herbs *Astilbe rivularis, Bergenia ciliata, Cassiope fastigiata* and *Thymus linearis* showed potent anti-herpes viral activity. The extracts of *Allium oreoprasum, Androsace strigilosa, Asparagus filicinus, Astilbe rivularis, Bergenia ciliata* and *Verbascum thapsus* exhibited strong anti-influenza viral activity. Plants *A. rivularis* and *B. ciliata* demonstrated remarkable activity against both viruses[5]. Several herbs are effective against influenza virus, herpes simplex virus, and coronaviruses[6,7]. The previous study on common essential oils also showed that, marjoram, clary sage and anise essential oils were most effective at reducing visible cytopathic effects of the anti-influenza (A/WS/33 virus). The current research effort on coronavirus is focusing on compounds of earlier research on severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), which also were caused by coronaviruses[8] . Active compounds of oils contained linalool, suggesting that this may have anti-influenza activity[9]. Triterpene glycosides saikosaponins (A, B2, C, and D) isolated from medicinal plants are also effective against coronavirus[10]. These natural compounds effectively prevent the early stage of HCoV-22E9 infection, including viral attachment and penetration. Extracts from plants have also been documented to display anti–SARS-CoV effect from a screening analysis using hundreds of Chinese medicinal herbs[11]. Natural inhibitors against the SARS-CoV enzymes, such as the nsP13 helicase and 3CL protease, have been identified on myricetin, scutellarein, and phenolic phytochemicals[11-13]. Other anti-CoV natural medicines include the aqueous extract of a medicinal plant which exhibited several antiviral mechanisms against SARS-CoV, such as inhibiting the viral 3CL protease and blocking the viral RNA-dependent RNA polymerase activity[14]. Recent outbreaks in coronavirus disease have significantly hampered public health due to the lack of exact an antiviral vaccine. The whole

genome of SARS-CoV-2 has 86% similarity with SARS-CoV[7]. Of the natural compounds screened against COVID-19, 13 that exist in traditional Chinese medicines were also found to have potential anti-2019-nCoV activity. Recently, 125 Chinese herbs were treated and found that 26 are classically cataloged as treating viral respiratory infections. Network pharmacology analysis predicted that the general in-vivo roles of these 26 herbal plants were related to regulating viral infection, immune/inflammation reactions and hypoxia response[15]. There is plenty of data supporting the effectiveness of herbs in treating viral infection but it is difficult to tell exactly how well herbs perform because in most cases they are administered with modern pills and some patients in critical condition are also supported with technical life support such as artificial lungs [16].

The high mutation rate of coronavirus has allowed the virus to continuously evolve to generate new strains that are resistant to the current commercially available antivirals. The structure of coronavirus is composed of RNA based proteins that contains amino and carboxyl groups located in the short NH2-terminal domain outside the virus and a long COOH terminus cytoplasmic domain inside the virion[17]. As the amino and carboxyl groups are functional components of this virus, it causes infection human cells of respiratory. The target to deactivate the coronavirus can be taken on the basis that, the natural compounds containing the hydroxyl (-OH) groups react chemically to deactivate the active components of the virus by esterification process.

METHODOLOGY

Literature study and research were done with great accuracy to analyze the existing research activities on antiviral herbs mainly against coronavirus to identify actual efficacy to increase the quality of this review. Major well-known bibliometric information sources studied are the Web of Science, Scopus, Mendeley and Google Scholar. Several keywords like name of plants, immunomodulatory, antiviral, coronavirus, COVID-19, Ayurvedic herbs, traditional medicine were chosen to obtain a large range of papers to be analyzed. An independent approach was used to conduct the literature review. The methodological activities involved during a literature review were; (1) designing the review concept, (2) conducting the review on publications such as review papers, research papers, bulletins, official website of related authorities, (3) analysis of previous publications and (4) writing up the review. The integrative literature review and paper preparation process was done from our own practical experience and influenced by various standards and guidelines suggested in the publications literature[18]. A final inventory of 175 research papers and articles and online information were made after sorting and then reviewed to bring the information on antiviral activity particularly with coronavirus infection and enhance host immunity against viral attack in the context of no specific treatment for COVID-19 available at this time.

1) Tinospora

The botanical name of Tinospora is *Tinospora cordifolia*, called Amrata, Guduchi in Sanskrit and Gurjo in Nepali. Plant stolon is commonly 0.6-5 cm in diameter young stems as mentioned in Ayurvedic Pharmacopoeia of India. Applications in fever, leprosy, anemia, obesity, diabetes, gout-arthritis, jaundice was described in Caraka Samhita and Ayurvedic Pharmacopoeia. The plant mainly contains alkaloids, glycosides, steroids, sesquiterpenoids, aliphatic compounds, essential oils, mixture of fatty acids and polysaccharides. The major phytoconstituent include tinosporine, tinosporide, tinosporaside, cordifolide, cordifol, heptacosanol, clerodane furano diterpene, diterpenoid furano lactone, tinosporidine, columbin, β-sitosterol. Berberine, palmatine, tembertarine, magniflorine, choline and tinosporin are reported from the stem of the plant[19] . A review shows that the plant is used for antiviral activity and immunomodulating activity[20] . Its consumption dose is given in Ayurvedic Pharmacopoeia as 3-6 g of the drug in powder form, 20-30 g of the drug for decoction.

Preclinical and clinical information on antiviral property of *T. cordifolia* is obtained and compared for the curative property against a broad spectrum of viral infections. *Tinospora* components have antiviral potentiality that decreases the recurrent resistance of human immunodeficiency virus (HIV) to antiretroviral therapy and improves the outcome of the therapy[21]. Anti-HIV effects of root extract were revealed by reduction in eosinophil count, stimulation of B lymphocytes, macrophages and polymorphonuclear leukocytes and hemoglobin percentage thus, revealing its promising role of application in the management of the virus-related disease[22,23]. Concentration level of methanolic extract of Tinospora powder 100µg/ml and 50µg/ml the percentage protection against oral herpes virus (HSV-1), offered is approximately 61.43 % and 23.22 % respectively[24]. Cordifolioside A 11-hydroxymustakone, N-methyl-2-pyrrolidone, N-formylannonain, magnoflorine, tinocordiside and syringin have been reported to possess immunomodulatory activity which support to fight against viral diseases[25]. The α-D-glucan of Tinospora activates human lymphocytes with the downstream synthesis of the pro- and anti-inflammatory cytokines, in vitro benefited as novel immune stimulator drug[26]. Dry stem crude extracts with a polyclonal B showed macrophages activation, repair and prevention of oxidative damage of cells [27] . Treatment with this extract (100 mg/kg body weight for 15 days) in carbon tetrachloride intoxicated rats was found a reduction in liver serum levels of SGOT, SGPT, ALP, bilirubin suggested that the remedy for the immune functions[28] . In several studies also, it has been shown to possess immunomodulatory properties[25, 29, 30] maintains the depleted levels of superoxide dismutase in liver[31] , antibody production in vivo [32] which ultimately enhances the capacity to fight against diseases including viral disease. Identification of the mechanism of action and structural activity relationship these

natural viral inhibitors could help the development of therapeutics to battle against coronavirus infection and reduce the risks of infection by enhancing the immune system.

2) Licorice

The botanical name of licorice is *Glycyrrhiza glabra*, called Yashtimadhu in Sanskrit and Jestimadhu in Nepali. The plant is commonly used in the treatment of common cold, sore throat, vomiting, acidity, gout, weakness, joint pain, ulcer, skin-related diseases. In Ayurveda and traditional medication licorice has been effectively used in the treatment of coughs, colds, flus, bronchitis, sore throat and laryngitis while dose generally taken as 2 grams in decoction form. In the ancient Ayurvedic system, more than 1250 preparations are described containing Yashtimadhu as one of its constituents[33]. It is also considered as an antiviral herb in WHO publication of monographs of medicinal plants. Licorice contains more than 20 triterpenoids and nearly 300 flavonoids. The extracts have been shown to possess a lot of medicinal properties due to presence of so many bioactive components, triterpene, saponins, flavonoids, alkaloids, glycyrrhizin, glycyrrhizic acid, glabridin, liquiritin, etc.

Research has assessed the antiviral potential of active compound of licorice glycyrrhizin against two clinical isolates of coronavirus (FFM-1 and FFM-2) from patients with SARS admitted to the clinical center where the glycyrrhizin sowed inhibiting replication of the SARS-associated virus suggesting that glycyrrhizin should be assessed for treatment of SARS virus is similar to coronavirus[34]. In another study, glycyrrhizin treatment inhibited the hepatitis C virus titer and caused 50% reduction of at the concentration of 14±2 μg/mL by inhibiting viral particles and their core gene expression[35]. Adhesion force and stress between cerebral capillary vessel endothelial cells and polymorph nuclear leukocytes were increased in herpes simplex virus infection by reducing adhesion force and stress between cerebral capillary vessel endothelial and polymorph nuclear[36]. Glycyrrhizin showed a significant improvement of coxsackievirus B3 (CVB3) induced myocarditis by reducing serological levels of cardiac enzymes and increasing survival rate and concluded that glycyrrhizin as a new therapeutic approach for the treatment of viral myocarditis [37] and also showed good immune stimulant and antiviral effects against duck hepatitis virus (DHV)[38]. It found that, glycyrrhizin is an effective antiviral compound against several viruses by weakening virus activity, such as inhibiting virus gene expression and replication, reducing adhesion force and stress, and reducing HMGB1 binding to DNA[39,40,41,42]. An independent study confirmed the antivirus activity of glycyrrhizin by plaque reduction assays and this study found that another Chinese herbal compound baicalin also had the anti-SARS activity[43]. Another compound of licorice 18β-glycyrrhetinic acid also inhibited rotavirus replication, which likely occurred at steps after virus entry [44]. This compound reduced rotavirus yields by 99% when it was added to

infected cultures post-viral adsorption. The levels of viral proteins VP2, VP6 and NSP2 were substantially reduced[45] . 18β-Glycyrrhetinic acid also showed potent anti-human respiratory syncytial virus (HRSV) activity. It inhibited HRSV mainly by internalization, stimulating interferon (IFN) secretion, and preventing viral attachment [46]. Glycyrrhizin and glycyrrhizic acid have been shown to inhibit the growth and cytopathology of numerous RNA and DNA viruses, including hepatitis A9 and C,[46] herpes zoster, HIV[47] . This evidences showing that active chemical constituents hold a strong promise for providing new molecules, which could be of immense medicinal applications in the drug discovery process for the research of new antiviral molecule focusing on coronavirus.

3) Chirata

The botanical name of the plant is *Swertia chirayita* (Roxb. *ex* Fleming) H. Karst, called Kirata, Kirataka, Kiratatikta in Sanskrit and Chiraito or Tito in Neplali. It is used in traditional medicine to treat numerous ailments and reported to have a wide spectrum of pharmacological properties[48]. This ethnomedicinal herb is known mostly for its bitter taste caused by the presence of different chemical constituents such as amarogentin, swerchirin, swertiamarin, and other bioactive compounds that are directly associated with human health welfare[49] . The plant generally taken as powder or decoction is prepared 1-3 gram powder and consumed in divided dose.

Several studies on chirata have been explored and found potential against lethal viral infections. Crude extract (1 gm/mL) at 1:64 dilution showed antiviral properties against Herpes simplex virus type-1 (HSV-1). Infected cell cultures treated with extract at various time intervals and tested failed to show amplification up to 72 hours against Herpes simplex virus type-1[50]. Using tissue culture technique average plaque reduction rates of active compounds mangiferin and isomangiferin against HSV-I were 56.8% and 69.5% respectively[51]. Mangiferin was also found to antagonize in vitro the cytopathic effect of HIV, act as a potent biological response modifier with antiviral effect[52]. Swerilactones H-K exhibits potent anti-hepatitis B virus activity against HBV DNA replication with IC_{50} values ranging from 1.53 to 5.34 μM[53]. Twenty six compounds of Chirata were evaluated for anti-hepatitis B virus (anti-HBV) activities on HepG 2.2.15 cells line in vitro, some compounds had shown inhibitory activity on hepatitis B surface antigen (HBsAg) secretion. Compounds has also exhibited activity against hepatitis B e antigen (HBeAg) secretion and possessed activity against HBV DNA replication on selected basis. Lignan glycoside (+)-cycloolivil-4'-O-β-d-glucopyranoside exhibited inhibition not only on the secretions of HBsAg and HBeAg, but also on HBV DNA replication activity[54]. Chirata holds the immense possibilities for research and development in Nepal for formulation of effective immunomodulatory remedy against various viruses including coronavirus. Therefore traditional medicine practice should be clubbed with scientific research facilitating modern drug

discovery on coronavirus particularly COVID-19 pandemic.

4) Basil

The botanical name of the plant is *Ocimum sanctum* L, and called Surasa in Sanskrit and Tulsi in Nepali. The genus Ocimum comprises 30 species which are found in tropical and subtropical regions. In Ayurvedic medicine it is used in common colds, headaches, stomach disorders, soreness, heart sickness, a range of poisoning, and malaria[55]. Basil has revealed the presence of five fatty acids, carotene, minerals, vitamins and it also contains volatile substances including estragol, linalool, eugenol, methyl chavicol, camphor and tannins, flavonoids, as well as nutrients[56, 57]. Many in vitro, animal and human studies attest to tulsi having multiple therapeutic actions including adaptogenic, antimicrobial, anti-inflammatory, cardioprotective, and immunomodulatory effects, and safe[58] . The dose is generally 10 g fresh tulsi leaf aqueous extract administered as once or four equal doses daily, or tincture solution 30 drops a day were administered as three equal doses daily. Many promising basil treatments exist for viral diseases with proof of their efficacy and safety in human trials. A 2-week controlled randomized study in which young adult volunteers were provided with nutrition bars fortified with 1 g of ethanolic tulsi leaf extract found that compared to control participants, the intervention group had significantly improved VO_2 max, less fatigue, reduced creatine kinase, and improved immune response to viral infection as indicated by the reduced load of human herpesvirus 6[59]. Clinical trials by giving daily 10 g of an aqueous extract of fresh tulsi leaves in patients with acute viral infections, with a study on patients with acute viral encephalitis reporting increased survival after 4 weeks in the tulsi group compared to a group given dexamethasone and a study on viral hepatitis reporting symptomatic improvement after 2 weeks[60,61] . A further study of asthmatic patients found that 500 mg of dried tulsi leaves taken three times daily improved vital capacity and provided relief of asthmatic symptoms within 3 days[62]. Significant increase in the levels of IFN-γ, IL-4 and percentages of T-helper cells and NK-cells were observed after 4 weeks in the tulsi extract intervention group in contrast to the placebo group ascertain the immunomodulatory role on healthy volunteers [63] .This ethnomedicinal herb studied that aqueous extract of at the oral doses of 100, 200 mg/kg/day in rats enhances the production of RBC, WBC, hemoglobin and also enhanced the production of antibodies without affecting the biochemical parameters[64], could support the defense to fight against flue and virus. Study of crude aqueous and ethanolic extracts yielded some compounds related to tulasi like apigenin, linalool and ursolic acid, exhibiting a broad spectrum of antiviral activities, especially against coxsackie virus B1 and enterovirus-71[65]. Considering the safety of basil and its availability in our backyard, this plant could be considered as an antiviral alternative, thus presenting immense scope for exploration and research in coronavirus. While promising, all of these studies conducted and our traditional literatures will determine

whether Tulsi is an effective antiviral herb and immunomodulatory remedy.

5) Ginger

The botanical name of ginger is *Zingiber officinale* Rosc, called Sunthi in Sanskrit and Aduwa in Nepali. It originated in South-East Asia and then used in many countries as a spice and condiment to add flavor to food[66] . From an Ayurvedic perspective, ginger is a superfood, particularly for digestion, respiration and the joints. Ginger has traditionally been used to cure common colds and throat infections and form an important constituent of Ayurvedic formulations. Ginger is widely used in Chinese, Ayurvedic and Tibb-Unani herbal medicines all over the world, since antiquity, for a wide array of unrelated ailments[67] . Volatile phytochemicals include mostly zingiberene, , β-sesquiphellandrene, bisabolene, farnesene, β-phellandrene, cineol, citral and non-volatile pungent compounds include gingerols, shogaols, and zingerone[68] . Ginger can be consumed as a fresh or dried root and is often prepared in teas, soft drinks. Most clinical research has used between 250 mg and 1 g of the powdered root in capsular form, taken one to four times daily [69] .

Traditional practices show that ginger has powerful antiviral effect. Research data also support that ginger and its constituents are useful as antiviral natural products. In ancient cultures, medical practitioners focused on herbs for promoting the immune systems of body. In many countries ginger and its products raise the immune system[70]. It is effective in hepatitis C virus (HCV) infection where viral clearance is affected[71,72,73]. Ginger enhances resistance to infectious disease by increasing non-specific and specific immune mechanisms thereby helps to reduce the losses caused by diseases. Mild, moderate and severe nausea was significantly lower in the ginger than the placebo group when randomized clinical trial ginger efficacy for the prevention of antiretroviral-induced nausea and vomiting was investigated[74] . Administering 120 mg of ginger extract daily for up to 21 days increases the number of days without ventilator support, the amount of nutrients consumed and reduces the time spent in intensive care units in people with the sudden respiratory system a failure[75]. There have been numerous studies on the efficacy of these compounds as antiviral agents[76,77]. Zingiberene and its phytoconstituents has biological activities such as antifever, antivirus and antigestation[78]. Components of ginger rhizomes are reported to contain potent compounds capable of suppressing allergic reactions and might be useful for the treatment and prevention of allergic diseases[79] . We therefore speculate that the phytochemicals or crude extract of ginger can be effective against different viruses and may be useful in coronavirus either directly inhibiting them or by boosting the immune system and required for specific mechanistic information.

6) Turmeric

The botanical name of turmeric is *Curcuma longa L.*, called Haridra in Sanskrit and Haledo/Besar in Nepali. In Ayurvedic medicine, turmeric is a well-documented treatment for various respiratory

conditions, runny nose, cough, and sinusitis[80]. The plants contain several secondary metabolites including curcuminoids, sesquiterpenes, and curcumin being the principal component of the yellow pigment and the major bioactive substance[81]. A review shows that curcumin as a multifaceted compound against human papilloma virus infection[82]. Turmeric powder mixed with black pepper is boiled in half cup water and taking with honey is beneficial in flue and cough.

The antiviral effect of active compound of turmeric, curcumin against hepatitis viruses has been investigated by several groups [83, 84, 85], inhibits hepatitis viruses gene expression and replication [86]. Several studies tested the effect of curcumin on different Influenza A virus, HIV and hepatitis C virus to inhibit virus uptake, replication and particle production[87,88,89]. A subsequent study confirmed this effect and explained it by curcumin's ability to modulate the features of lipid bilayers[90]. Curcumin treatment reduces lung inflammation due to influenza A virus infection in mice[88, 89]. Several studies found that low micro molar, not cytotoxic amounts of curcumin dampened HSV-1 and HSV-2 infectivity *in vitro* and *in vivo* [91,92,93]. Curcumin formulations could potentially be used to prevent sexually-transmitted HPV infections or to treat cervical dysplasia caused by the virus[94]. The use of curcumin against respiratory syncytial virus infections revealed[95]. Studies revealed that curcumin blocks the entry of chikungunya virus[96]. Curcumin was also evaluated for activity against severe acute respiratory syndrome-associated coronavirus (SARS-CoV) activities using a cell-based assay exhibited strong anti-SARS-CoV effects[97] . Because it has been known for many years to have excellent therapeutic potential against various diseases, it may also help to improve the health immune system in recovery from coronavirus and a good candidate on antiviral activities.

7) Garlic

The botanical name of garlic is *Allium sativum* L, called Lashunam in Sanskrit and Lasun in Nepli. S-allylcysteine, sallylmercaptocysteine, allixin, and selenium are antioxidant compounds of garlic. Volatile garlic oil consists of the diallyl, allylmethyl, and dimethyl mono- to hexa- sulfides [98]. Ancient Chinese and Indian medicine recommended garlic to aid respiration. Ayurvedic practitioners most often use garlic as tea, powder, juice and medicated oil. Ayurveda recognizes garlics effect on the respiratory system, rejuvenating herb along with several other uses.

The few studies on antiviral property of garlic extract showed *in-vitro* activity against influenza A and B (Fenwick and Hanley, 1985), cytomegalovirus [99, 100] , rhinovirus, HIV, herpes simplex virus-1[101], herpes simplex virus-2[102], viral pneumonia, and rotavirus. Allicin, diallyl trisulfide and ajoene have all been shown to be active[102, 103]. Ajoene acts by inhibiting the integrin-dependent processes in HIV infections[104]. Allyl alcohol and diallyl disulfide have also proven effective against HIV-infected cells[105]. The investigation revealed 24 occurrences of the common cold in the garlic given group compared

with 65 in the placebo group, resulting in fewer days of illness in the garlic group compared with the placebo group[106] . The growth of histamine-producing bacteria was inhibited by garlic and turmeric extracts at a 5% concentration[107] . Garlic has long been claimed as possessing qualities that aid in the prevention of various illnesses, including colds and flu, and scientific evidence supporting such claims is limited. Though the exact mechanism of all ingredients and their long-term effects on virus is not fully understood but traditional medicine and ethnobotanical practices supporting that garlic extracts are taken as immunobooster and manage defense against diseases can be useful in viral illnesses.

8) Ashawagandha

The botanical name of Ashawagandha is *Withania somnifera* (L.) Dunal, also called Ashvagandha in Sanskrit and Ashwagandha in Nepali. The roots of the plant are categorised as rasayanas, which are reputed to promote health and longevity by augmenting defense against disease, arresting the ageing process, revitalising the body in debilitated conditions, increasing the capability of the individual to resist adverse environmental factors and by creating a sense of mental wellbeing. The biologically active chemical constituents are alkaloids including ashwagandhine, cuscohygrine, anahygrine, tropine etc, steroidal compounds, including ergostane type steroidallactones, withaferin A, withanolides A, withasomniferin-A, withasomidienone, withasomniferols A-C, withanone etc. Other constituents include saponins containing an additional acyl group like sitoindoside VII and VIII, and withanolides[108].

The studies on withania as immunomodulator has been extensively supporting as a better alternative to fight against the devastating fungal disease. Significant increases in hemoglobin concentration, red blood cell count, white blood cell count, platelet count, significant increase of antibody, and body weight, enhancement in phagocytic activity of peritoneal macrophages confirm the immunomodulatory activity of withania extract in indigenous medicine[109-113]. It possesses the power of combating disease caused by Herpes Simplex Virus among African tribes [114], and influenza virus[115]. Studies support the fact that holds important place as a potent antiviral agent and hence, plays a significant role in inhibiting viral disease.

9) Moringa

The botanical name is *Moringa oleifera* Linn, called as Drumstick tree, Horseradhish tree or Miracle tree in English, Shobhanjana in Sanskrit and Sheetal Chini in Nepali [116]. It is native to the sub-Himalayan tracts of India, Pakistan, Bangladesh and Afghanistan[117]. Various parts of this plant such as the leaves, seed, bark, fruit and flowers has been advocated for nutritional, medicinal and industrial uses[116, 118, 119]. According to Ayurveda, the leaves of the moringa tree prevents 300 diseases and combat malnutrition, especially among infants and nursing mothers[117, 120]. In Siddha medicines, seeds of moringa are used to treat erectile dysfunction [121, 122]. In African traditional medicine, the plant is popularly used

against AIDS and related secondary infections associated with HIV[123,124]. Moringa consists of mainly flavonoids, isothiocyanates glycoside, glucosinolates, sterols, terpenoids, and proteins, minerals [116, 125, 126].

The isothiocyanate glycoside and flavonoids have tremendous antimicrobial and antiviral properties [116, 119, 127-133]. Unfortunately, many of these reports of efficacy in human beings are not supported by placebo-controlled, randomized clinical trials. Moringa leaves has been reported antiviral activity against Equine herpes virus (double-stranded DNA virus), Herpes simplex virus (Double stranded DNA virus), Epstein bar virus (double-stranded DNA virus)[134] , Newcastle Disease Virus[135, 136] , Hepatitis virus (Ds DNA virus)[137] , Rhinovirus (+ sense ss RNA virus) 138 , HIV (Retro RNA virus)[124] , Smallpox (DNA), Foot and mouth disease virus (FMDV) (+ sense ss RNA virus), Infectious bursal disease virus, Bovine herpes virus type-1 [139] , Chikungunya virus, Poliovirus type-1 [130] and Duck plague virus[139]. It has been reported that quercetin derivatives found in MO target the initial stages of the virus replication cycle of porcine epidemic diarrhea virus (PEDV) [140] . So it is quite evident that moringa leaves have broad-spectrum antiviral activity, good for immunity and fighting viruses and the isolated bioactive compound could be used as novel drug candidate or lead compound for antiviral drug discovery.

10) Nepalese Pepper

The botanical name of Nepalese pepper is *Zanthoxylum armatum* DC, also called as Tejowati in Sanskrit and commonly called Timur in Nepali. The fruits are very useful for cold & cough, tonsillitis, headache and toothache in Ayurvedic medicinal system. The various studies have reported that the different parts of this plant like leaves, fruits, stem, bark and seeds possessed alkaloids (Berberine, Dictamine and g & b-Fagarine), steroids (β-Sitosterol-β-D glucoside), phenolics, lignins (Asarinin and Sesamin), coumarins (Bergapten and Xanthyletin), terpenoids (Linalool, Limonene, α & β-Phellandrene, Myrcene, p-Cymene, Camphene and β- Amyrin) and flavonoids (Vitexin and Tambulin) as major biologically active chemical constituents [141- 143] .

Therefore, the presence of such bioactive constituents in different parts of timur has associated to show several pharmacological and biological activities like antimicrobial, antiviral. Previous studies have shown that Timur possesses an eminent *in-vitro* antiviral activity against several viruses. The extracts (methanol) of fruits have been utilized to show good efficacy against Herpes simplex virus type 1(HSV-1) and influenza virus A [5]. The extract (aqueous) of the leaves exhibited antiprotozoal effect [144] . Linalool as a one of the major compounds in oil is considered to be antiviral, antibacterial and immune system stimulant[145]. Similarly in another study the linalool showed the bronchodilator and antiasthmatic properties (Downregulates the in histamine and OVA-induced allergens in guinea pigs and mice[146].

11) Cinnamon

The botanical name of Cinnamon is *Cinnamomum zeylanicum*, also called Thwak in Sanskrit and Dalchini in Nepali. Cinnamon has also been traditionally used as tooth powder and to treat toothaches, dental problems, oral microbiota, and bad breathe[147] and also as a spice and flavoring agent, as mouth refreshing effects. Cinnamon consists of a variety of resinous compounds, including cinnamaldehyde, cinnamate, cinnamic acid, and numerous essential oils[148]. The spicy taste and fragrance are due to the presence of cinnamaldehyde and occur due to the absorption of oxygen[149] .The presence of a wide range of essential oils, such as *trans*-cinnamaldehyde, cinnamyl acetate, eugenol, L-borneol, caryophyllene oxide, b-caryophyllene, L-bornyl acetate, E-nerolidol, α-cubebene, α-terpineol, terpinolene, and α-thujene, has been reported[150].

It was investigated the inhibitory effect of one of the principal constituents of essential oil derived from Cinnamon called trans-cinnamaldehyde. Inhalation of trans-cinnamaldehyde caused virus yield reduction by 1 log in bronchoalveolar lavage fluid on day 6 after infection, compared with that of the untreated control group [151] . *Cinnamon* components have antiviral potentiality that is nanoparticles applications recently extended to the development of antivirals to inhibit viral infections. The extract of the barks of Cinnamomum showed inhibitory activity against the H7N3 virus in infected Vero cells[152]. Another study showed that cinnamon essential oil and powder had antiviral activity while blended with other essential oils[153]. The evidences and identification of the mechanism of action and structural activity relationship of these active natural viral inhibitors chemical compounds could help the immense medicinal development of therapeutics against coronavirus infection and reduce the risks of infection by enhancing the immune system. Cinnamon leaves and bark was able to inhibit the propagation of human rotavirus 32.4% and 33.9% respectively[154].

12) Indian Gooseberry

The botanical name of indian gooseberry is *Phyllanthus emblica*, also known as Amalaki in Sanskrit and Amala in Nepali. It is one of the popular medicinal plants in folklore medicine, Ayurveda and Unani[155] . It is also mentioned in Rigveda, which is supposed to be the oldest repository of human knowledge[156]. According to Ayurveda system of medicine it increases defense against diseases [157]. The fruit is a rich source of Vitamin C and commonly used to make pickles, preserves and jellies[158]. The major phytochemicals are ascorbic acid, flavonoids, ellagic acid, gallic acid, chebulanin, and chebulagic acid [159, 160]. The polyphenols found especially tannins and flavonoids are key components for major bioactivities[161].

A plethora of research on the antiviral activity of the fruits of this plant show that, a polyphenolic compound 1,2,4,6-tetra-O-galloyl- β-D-glucose (1246TGG) isolated from fruit showed in-vitro

inhibition of Herpes simplex virus type 1 (HSV-1) and type -2(HSV-2) infection. The mechanism of inhibition was possibly due to inactivation of extracellular viral particles and inhibition of viral biosynthesis in host cells [162]. 1246TGG also decreased the levels of HBsAg and HBeAg levels in HepG2.2.15 cell culture supernatant, showing promising anti-hepatitis B virus (HBV) activity[163]. Phyllaemblicin B, a sesquiterpenoids glycoside found in fruits inhibited Coxsackie virus B3 (CVB3)-mediated cytopathic effects on HeLa cells with an IC50 value of 7.75 ± 0.15 μg/mL showing anti-Coxsackie B virus activity [164,165]. 1mg/ml concentration of aqueous and hexane extract of fruit showed 91% and 89% Anti HIV reverse transcriptase activity respectively [166]. The sesquiterpenoid glycoside dimer, Phyllaemblicins G6 isolated from roots showed potential anti-hepatitis B virus (HBV) activities, with IC50 of 8.53 ± 0.97 and 5.68 ± 1.75 μM towards the HBV surface antigen (HBsAg) and HBV excreted antigen (HBeAg) secretion, respectively[167]. The fruit extract showed dose-and time-dependent down-regulation Activator Protein-1 (AP-1) activity and suppression of human papillomavirus (HPV) transcription that resulted in growth inhibition of cervical cancer cells[168]. It is necessary to assess the usefulness of this herb by isolating and identifying the bioactive antiviral principle(s) and understand their mechanism of action. Indian gooseberry seems likely safe for most people when consumed in amounts found in foods, can be used as a supplement to maintain the immune system and fight against viral sickens.

WAY FORWARD

Herbal medicines and purified natural products provide a rich resource for novel antiviral drug development[169]. Ayurvedic herbs have enough possibilities to be employed both for the prevention and treatment of COVID-19[170]. Similarly Traditional Chinese Medicine (TCM) has also been employed in COVID-19 cases suggesting as remedies [171]. TCM can cure COVID-19 pneumonia, and also shows that the role of TCM in blocking the progress of COVID-19 pneumonia [172]. The herbs described in Ayurveda and TCM are reviewed for the reason that these are known to be broad-spectrum antivirals and protease inhibitors as well as they also boost the immunity to fight against flu-like diseased live COVID-19. These herbs either in a single form or in combination consumed for centuries in tribal therapy as well as in alternative medicine are largely based on good results till date, when subjected to rigorous scientific investigation. Many governments of Asian countries are also advising their population to consume herbal medicines to maintain the immune system and to reduce the infection risk from COVID-19. The scientific evidence further support the herbal consumption for some of the viral infectious diseases to maintain the overall immune health of people who are infected with COVID-19. Researchers suggested that if this approach of herbal therapy brought into practice and validated, the rapid immunological response of such herbs or extracts could be effective and timely in the fight against COVID-19. The

extensive utilization of Ayurvedic and TCM herbal formulations, current use of herbs in daily practices, scientific data on antiviral properties, immune response studies, and general hygiene measure by using such natural resources can be taken as a preliminary data so that larger randomized multicenter clinical trials of further studies may be designed for SARS-CoV-2. Researchers would bring a new SARS-CoV-2-based vaccine but while waiting for a specific vaccine, a herbal consumption approach for immunotherapies could represent an option to fight against SARS-CoV-2[14,15,22,173]. As efforts are underway to find treatment for COVID-19, caution must be taken against misinformation about the effectiveness of certain remedies[174]. One of ways of holistic management of health for the prevention of respiratory illness of any kind, is to make a decoction of the selected herbs, allow it to cool until just warm, and add honey just before drinking. Above mentioned herb are also described for the treatment of several disease in Charak Samhita, an oldest and the most authentic record on Ayurveda[175]. In the Charak Samhita, there is a specific chapter on 'krimi' i.e. infections. In the chapter, there is a description of Sleshma Krimi to treat the respiratory system related illnesses.

CONCLUSION

We conclude that the research on several Ayurvedic herbs, which also are locally available in Nepal possesses antiviral properties. In the context of treatment vaccine of COVID-19 could be years away, herbal medicines could be useful for the prevention of COVID-19 infection and symptomatic management. The traditional practices and scientific evidence of the above described herbs and their phytochemicals against lethal viral infections *in-vivo* and *in-vitro* studies supports the natural product for drug discovery particularly against coronavirus.

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