

Scientific aspect of common medicinal plants to fight against COVID-19

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Abstract

Since the last months of 2019 the whole world is facing a pandemic called COVID-19 (Novel Corona Virus). In a country like India which is densely populated, any infectious disease can spread rapidly. After disastrous first wave, we have already entered the second wave of the pandemic. As the vaccines are not such effective for new strains of the virus and also will not be available for all the people in a very short duration of time, so there should be an alternative to boost our immune system to reduce the chance of getting infected. Indian household have been known to grow various medicinal plants (Tulsi, Kalmegh, Neem, Garlic, Aloe vera, Ginger, Paan, Turmeric, Ashwagandha etc.) since ages. These traditional medicinal or herbal plants are enriched with phytochemicals that have antibacterial, antiviral, antipyretic, anti-inflammatory, antithyroid, antitumor and antioxidative properties that enhance immunity by many folds. Various scientific studies have been done on phytoconstituents of all the above-mentioned medicinal plants to find scientific evidence. The Ministry of AYUSH recommended the use of Kadha, the mixture of *Ocimum tenuiflorum* (Holy Basil or Tulsi), *Cinnamomum verum* (Cinnamon), *Piper nigrum* (Black Pepper), *Zingiber officinale* (Ginger), *Vitis vinifera* (Grape Vine) and *Curcuma longa* (Turmeric) in golden milk as a preventive measure to boost immunity and to inhibit the severity of infection caused by a novel Coronavirus. From various literature surveys we suggest that ayurvedic and medicinal plants have beneficial properties to cure infectious and other diseases as well as may help in prevention of COVID-19.

Introduction

COVID 19 has become the biggest threat to the mankind. A deadliest microorganism-Corona Virus is in the topic of discussion since December 2019 when Wuhan, a city in China reported the first case of SARS-CoV2. The WHO declared it initially a public health emergency of international concern and later pandemic where the COVID-19 symptoms include fever, sneezing, diarrhea, dry cough, malaise, respiratory distress, and shortness of breath. This virus has infected over 100 million people (181,532,691 up to 27th June 2021) in the world within one and half year and more than 3.9 million (3,932,442 up to 27th June 2021) of people have succumbed to it. The corona virus has been found to infect anyone especially older people and people with different co morbidity such as diabetes, kidney disorder, chronic obstructive pulmonary disease (COPD), chronic bronchitis, hypertension, cerebral infraction, Parkinson's disease, cancer etc. are considered to be at highest risk in contracting the virus and difficult to be recovered due to lower immune responses. Apart from the mandatory vaccination, immunity boosting is a major prophylactic measure against Covid 19 and multiple pathogenic conditions as well as maintaining optimum health.

This virus is a member of beta corona virus and found to be a similar with the severe acute respiratory syndrome corona virus (SARS-CoV) and the Middle Eastern respiratory syndrome corona virus (MERS-CoV) outbreak happened in 2012-2013 in its pathogenicity and clinical spectrum. This virus belongs to the family of coronaviridae and an enveloped positive stranded RNA virus. Their entire replication cycle takes place in cytoplasm. It can enter into the host cell through interaction between the S protein of the virus species and the receptor of the host cell. It will bind with the angiotensin-converting enzyme2 receptor from the host cell to create a suitable habitation for viral replication.

Naturally derived compounds are always considered as the worthy prophylactic and therapeutic alternative for several diseases. According to a study, from 1940 to 2014, 49% of all small molecules approved by the U.S. Food and Drug Administration (FDA) were natural products or their derivatives (Newman and Cragg

2016). Ayurveda is an ancient science and it is not only considered as an ethnomedicine but also as a complete medical system for maintaining a healthy and happy living. It concerns with the consumption of different gifts of nature (herbal concoction or individual herb) as a daily and/or seasonal regime for the maintenance of healthy lifestyle. It promotes the awareness of uplifting ones immunity by a regular consumption of different herbs or plants and their products in a particular amount which are easily available in most of household of the society depending on the geospatial habitation. Herbal exploration is continuously performed for the immunity improvement against corona virus type of diseases. Different spices and herbs have antioxidant, antimicrobial properties along with effects on physiological and biochemical constituents within the human body resulting into benefits of human immunity. Botanical ingredients contain many bioactive compounds such as flavonoids, phenolic compounds, sulfur-containing compounds, tannins, alkaloids, and phenolic diterpenes etc which have prophylactic benefits. India recognized six systems of medicine or AYUSH (Ayurveda, Yoga, Unani, Siddha and Homeopathy) and an advisory has been issued where the usage of Kadha or herbal tea which is composed of *Ocimum tenuiflorum* (Tulsi), *Cinnamomum verum* (Dalchini), *Piper nigrum* (Kalimirch), *Zingiber officinale* (Shunthi) and *Vitis vinifera* (Munakka) has been recommended. It is considered as a self-care regime which can develop immunity against severe infections caused by corona virus. It is also recommended the included spices such as turmeric, cumin, coriander, and garlic which are usual ingredients of Indian culinary along with incorporation of balanced nutritional food with special importance to protein uptake and easy digestion. Use of lemon to provide Vitamin C and antioxidant and golden milk (milk with pinch of turmeric) have also been recommended.

Hence in this present study we will discuss about the scientific approaches to identify the effects of individual phytoconstituents and their combination as recommended by Ministry of AYUSH, Government of India to maintain/boost the natural immunity by Gene-Set Enrichment Analysis (GSEA) and network pharmacology approaches.

Antiviral Properties of Herbs and Spices:

***Curcuma longa* L. (Turmeric):**

Turmeric (*Curcuma longa* L.) belongs to the family of ginger (Zingiberaceae) and natively grows in India and Southeast Asia. A natural polyphenol Curcumin that is isolated from turmeric (*Curcuma longa*) that has been used as a traditional medicine since ages in Asian countries for treating various disorders. Curcumin is reported as a dynamic antiviral that hinders the replication pathway of viruses. Curcumin plays a major role in targeting various cellular pathways, thus inhibiting the growth, and replication of viruses which makes it an ideal component as an anti-viral drug. According to the molecular docking study by Utomo et al. (2020), it is reported that the curcumin binds and inhibits the target receptors including SARS-CoV-2 protease, spike glycoprotein RBD, and PD-ACE2, which are involved in virus infection.

***Zingiber officinale* (Ginger):**

Ginger is one of the vital medicinal plants which occur naturally in various countries. Ginger, *Zingiber officinale*, belongs to family Zingiberaceae and the other members of this plant family are turmeric, cardamom, and galangal. The plant belongs to Southeast Asia and is cultivated in different parts of the world including India. Ginger (*Zingiber officinale*) is known as Sunthi in Ayurveda. Ginger is a rich source of bioactive compounds including phenolic groups, alkaloids, and steroids, which have important medicinal effect. The chief aromatic agent of the rhizome is the zingiberol. Many studies proved that the ginger and its bioactive compounds showed effective antiviral activity against SARS-CoV-2, Influenza virus, Human respiratory syncytial virus. Ahkam et al. (2020) studied the potential of bioactive compounds, like, gingerone A, gingerol, geraniol, shogaol, zingiberene, zingiberenol, and zingerone from Ginger as anti-SARSCoV-2 for their interaction to spike and main protease (Mpro) protein based on molecular docking study. From the study they found that the bioactive compounds of ginger block the spike (S) protein from binding to the ACE2 receptor or act as an inhibitor for Mpro. The S protein is responsible for SARS-CoV-2 entry during the infection which binds with angiotensin-converting enzyme 2 (ACE2) receptor from the host cell to generate an appropriate environment for viral replication (Walls et al. 2020).

***Cinnamomum cassia* (Cinnamon):**

Cinnamon is obtained from the bark of its young branches which is used all around the world as spices. It is used as an essential component for medical products and has high economic value. It is used for several conditions such as: toothache, fever, leukorrhea, common cold, and headache. It has also been reported that the

regular use of cinnamon averts throat infections (Hajimonfarednejad et al. 2019). Several researches have shown the antimicrobial, antiviral, antifungal, antioxidant, antihypertensive, antidiabetic, antitumor, gastroprotective, and immunomodulatory effects of cinnamon (Shen et al. 2012). They found that the hydroalcoholic extract of cinnamon was effective in minimizing the viral titer of HSV-1 by preventing the attachment of virus to the cells.

***Syzygium aromaticum* (Clove):**

Clove (*Syzygium aromaticum*), belonging to the family Myrtaceae, is globally used as an antiseptic against contagious diseases due to its antimicrobial activity against oral bacteria. The main bioactive component of clove is eugenol. Eugenol exhibits broad antimicrobial activities against both Gram-positive, Gram-negative, and acid-fast bacteria, as well as fungi. Eugenol, a compound isolated from the herbal extracts of *S. aromaticum*, and *Geum japonicum*, was identified as anti-Herpes Simplex Virus compound at 5 µg/mL concentration. The inhibitory action of eugenol is on the viral DNA synthesis by acting as a selective inhibitor of the HSV-1 DNA polymerase and eugenol on viral replication and reducing infection (Kurokawa et al. 1998). The WHO has given the acceptable daily uptake of clove in humans is 2.5 mg/kg body weight (Ogunwande et al. 2005).

***Piper nigrum* (Black pepper):**

Piper is a member of family Piperaceae and considered as the king of spices due to its pungent smell. Piperine, a dynamic alkaloid of black pepper, is widely used in the as conventional system of medicine (Ayurveda, Siddha, Unani, and Tibetan). It contains major pungent alkaloid piperine (1-peperoyl piperidine) which is known to possess many interesting pharmacological properties such as antihypertensive, anti-Alzheimer's, anti-inflammatory, antioxidant, analgesic, antimicrobial, and so on (Damanhour and Ahmad 2014; Yoo et al. 2019; Tiwari et al. 2020). The study evaluated the antiviral activity of *Piper nigrum* in chloroform and methanolic extracts against vesicular stomatitis virus (an enteric virus) and human parainfluenza virus on human cell lines. They found that the anti-viral property of *Piper nigrum* is higher in chloroform extract due to the presence of higher content of alkaloids. Rajagopal et al. (2020) in a docking based study reported that the bioactive compounds from black pepper such as piperdardiine and piperanine are considerably active against COVID-19, which can be further used for its treatment.

***Ocimum basilicum* L. (Basil):**

Ocimum basilicum L. (OB) is a popular medicinal herb of the family Labiatae. Numerous scientific studies showed that the aqueous and methanol extract of leaf and seed oil of basil enhances immune response by increasing T-helper and natural killer cells, lymphocyte count, phagocytic activity, neutrophil count, antibody titer, and so on against the variety of infection as a defense mechanism (Jamshidi and Cohen 2017; Pattanayak et al. 2010). Extracts of OB showed a broad spectrum of anti-DNA and RNA virus activities also. Three phytochemical compounds of tulsi, namely, vicenin, sorientin 4'-O-glucoside 2''-O-phydroxy-benzoate, and ursolic acid showed inhibition of main protease of SARS-CoV-2 in a molecular docking study.

***Allium sativum* L. (Garlic):**

Allium sativum L. (Garlic) family Liliaceae is originally from Asia but it is also cultivated globally. Garlic is having high nutritive value, used as a flavour enhancer, and also helps indigestion. Garlic is having a wide range of pharmacological effects with low toxicity such as anti-inflammatory, antioxidant, antifungal, etc. (Alam et al. 2016). Antiviral activity of garlic extract has been studied against influenza virus A/H1N1 in cell culture and it was found that it inhibits the virus penetration and proliferation in cell culture (Mehrbood et al. 2009). Studies showed that garlic extract showed inhibitory activity on infectious bronchitis virus (IBV-a coronavirus) in the chicken embryo (Shojai et al. 2016).

***Azadirachta indica* (Neem):**

Indica is a fast growing evergreen herb belonging to the family Meliaceae. Due to its already proven antiviral properties and effectiveness, many scientists have started research on neem for discovering drugs against SARS-COV-2. Natural bioactive compounds, namely, methyl eugenol, oleanolic acid. These potential bioactive compounds function as effective inhibitors of SARS-CoV-2 by binding to the spike glycoprotein, RNA polymerase, and/or its protease which results in the prevention of both viral attachment and replication (Kumar 2020). Approximately 20 compounds isolated from neem leaves extract showed high binding affinity against COVID-19 main protease protein which is the key protein for viral replication (Shanmuga 2020).

***Tinospora cordifolia* (Giloy):**

Tinospora cordifolia (giloy) is a member of the family of Menispermaceae and is usually found in Asian countries like India, Sri Lanka, Myanmar, and China. Pruthvish and Gopinatha (2018) reported that the crude extract of dry stem of *T. cordifolia* showed antiviral activity against herpes simplex virus which was evaluated by MTT assay. Tinocordiside, one of the phytochemicals of giloy, showed inhibition of main protease of SARS-CoV-2 in a molecular docking study (Shree et al. 2020). Berberine, Isocolumbin, Magnoflorine, and Tinocordiside compounds isolated from Giloy showed high binding efficacy against all the four key SARS-CoV-2 target surface glycoprotein (6VSB), RNA dependent RNA polymerase (6M71), receptor-binding domain (6M0J), and main protease (6Y84) involved in virus attachment and replication (Sagar and Kumar 2020).

***Vitis vinifera* (Common Grape vine):**

Vitis vinifera, the common grape vine, is a species of flowering plant, native to the Mediterranean region, Central Europe, and southwestern Asia, from Morocco and Portugal north to southern Germany and east to northern Iran. In traditional medicine of India *V. vinifera* is used in prescriptions for cough, respiratory tract catarrh, subacute cases of enlarged liver and spleen, as well as in alcohol-based tonics.

Conclusion

Recently, the ministry of AYUSH has advised using Kadha (herbal tea/decoction) composing basil, cinnamon, black pepper, dry ginger, and raisin and golden milk as immunity booster against COVID-19. Due to the complex composition of multiple phytoconstituents from all these medicinal plants, the mixture can control multiple proteins and can help to boost immunity which can be explained via network pharmacology and gene-set enrichment analysis. Network pharmacology and gene set enrichment analysis are well-known approaches to detect the disease targets, lead hit molecules and controlled pathways via “multiple component-protein interactions”. Boosting immunity includes the modulation of various proteins which are involved in the homeostatic regulation. In recent studies, the modulation of multiple pathways which are related to the immune system and infectious/non-infectious diseases are identified. Patients suffering from infectious/non-infectious diseases with weakened immune response; are at higher risk to be affected by COVID-19. So, the combined action of herbal tea and golden milk recommended by the ministry of AYUSH is not limited to boosting of the immunity but also may regulate other pathways that are involved in pathogenesis of multiple diseases and also provides beneficial effects to the patients with diabetes and hypertension.

AS the ministry of AYUSH advised oral intake of Kadha and golden milk, the studies attempted to detect the possible lead hits to get absorbed from the human intestinal tract in which most of the compounds were predicted to be absorbed from the gastrointestinal tract. One of the major limitations of the present studies is neither in-vitro nor in-vivo experimental data are provided to confirm immune-modulatory and anti-viral activities. Further, one part of the studies could be that the anti-covid potential of these formulations were not measured in experimental studies to validate the findings from above in-silico analysis.

As per survey study, most people were taking Kadha only one time a day and they were using ginger, clove, cinnamon, black pepper, and tulsi as main ingredients in Kadha. So, scientists analyzed that cinnamon, black pepper, tulsi, and turmeric play vital role against SARS-CoV-2 (COVID-19) and also included other viral infections, which was also supported by some other recent studies mentioned in Tables.

According to ASSOCHAM, India dipstick study spices export from India went up by 23% during COVID-19 in June 2020) compared to the export in June 2019. Major Indian spices that are exported abroad include coriander, cumin, fennel, fenugreek, nutmeg, pepper, ginger, mint, spice oils, cardamom, and turmeric products. The main countries where the spices are being imported include the Australia, Bangladesh, Canada, China, France, Germany, Italy, Iran, Singapore, United States and United Kingdom. It shows that the world is benefitted by the medicinal plants and spices of India.

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