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Review Article

Potential role of herbal medicinal agents against COVID-19 infection

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ABSTRACT

In December 2019, a novel infection called Corona virus disease (COVID-19) was first detected in Wuhan, China; caused by severe acute respiratory syndrome Corona virus 2 (SARS-CoV-2).

On 11th March, 2020, the World Health Organization declared COVID-19 infection a pandemic. Since then the scientific community around the world is trying to decipher this infection to control it better. We have been successful in formulating the vaccine against it in record time, but during this course, it has taken a huge toll of human lives leaving behind people who got infected with various side effects of the infection. In the absence of any definitive treatment, many alternative modes of management systems have appeared. Various herbal agents appear to have a potential role in prevention and management of this infection. In the limited time so far, several studies have been conducted which have shown positive results but also highlights their potential drawbacks with insufficient scientific evidence. This review describes the potential role of common herbal agents as possible means of management of this infection and the need of further research in this direction where these traditional and relatively safe methods could be integrated in the management schemes of various chronic infections and diseases.

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1. Introduction

In December 2019, a novel infection called Coronavirus disease (COVID-19) was first detected in Wuhan, China; caused by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) which mainly affects the respiratory system causing disease ranging from asymptomatic infections to respiratory distress and death. The World Health Organization (WHO) declared it as a public health emergency of international concern on 30th January'2020. On March 11th 2020, COVID-19 was declared a pandemic by WHO, calling all the nations to take aggressive steps to control its transmission.¹ The outbreak challenged the healthcare systems globally. During the initial days, the

medical fraternity was struggling hard to handle the cases which were causing devastation to the mankind at a catastrophic rate. As of 31st May'2022; about 523,218,741 cases were reported and 6,312,141 deaths have been registered due to COVID-19 infection world over.² India reported 43,158,582 Coronavirus cases and about 524,630 deaths have been registered due to COVID-19 infection by 31st May'2022.³

It took a long time for the researchers and the clinicians to understand the disease. The major challenge was the novelty of this virus and the infection. On daily basis, guidelines were being formulated by the world's scientific forums to understand the disease, to understand the means to prevent its transmission and finally to manage the disease. Currently, the administration of vaccines against this infection and the various public health prevention

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measures such as use of masks, social distancing, and hand hygiene remain the mainstay of COVID-19 transmission control measure.

2. COVID-19: Where do we stand now?

The genetic sequence of SARS-Cov-2 was published on January 11, 2020 and the scientific community world over got into understanding the nature of this virus. The pathogenesis of COVID-19 infection involves activation of inflammatory immune response, leading to cytokine storm, acute respiratory distress syndrome multi-organ dysfunction, and ultimately death in severe cases. In most of the cases, the infection affects the people with compromised immune status, elderly or those having comorbidities leading to adverse outcomes and grave prognosis ultimately causing majority of the deaths. Thus managing such patients requires means to improve the immunity.

India began its vaccination program on January 16th 2021. After the initial slow uptake, India exhibited remarkable vaccination rate. On 6th August 2021, India crossed the 500 million dose milestone within 6 months from the onset of vaccination program. As of 30th May'2022, about 73% of the Indian population had received at least 1 dose of vaccine and about 65% of the population was fully vaccinated.⁴ The devastating second wave caused by the Delta variant caused maximum mortality in India during the months of April 2021 and onwards leaving everyone off guard. The exponential increases in the cases lead to the breakdown of our medical infrastructure. Many were devoid of the medical care due to shortage of medical facilities and admissions in the hospitals. The number of newly established COVID care centers and hospital could not keep up with the number of infected patients requiring hospital care. The infection was so severe and contagious that home isolation and home care was also proving insufficient. It was difficult to obtain consultations with the doctors. This led to the introduction of 'WhatsApp Medicine' where people were circulating various authentic and inauthentic information even prescriptions on WhatsApp among families and friends.

In the absence of any targeted treatment against the causative virus, very soon majority of the people started switching towards alternative medicine modalities. During this 'COVID age' we witnessed how the importance of yoga and meditation regained its importance. Scientific evidence proves that these age-old traditional practices helps in improving the oxygen saturation, reduction of the catabolic process of cell deterioration and strengthens the immune system. Concomitantly, there was re-emergence of allied medicinal therapies with the increased use of various herbal medications as preventive and therapeutic agents.

Various management methods to prevent and treat this infection in the form of using various herbal agents, most of

which we use in our foods; started circulating. Even those who believed in allopathic medicines, in the absence of any recommended or guaranteed medicine to treat this infection; switched to various herbal agents. People started using them due to the fact that they would not cause any ill effects even if they don't provide any benefit.

The common herbs and natural products which were recommended to improve the immunity during COVID times as preventive and therapeutic agents were honey, black pepper, black cumin, lemon, ginger, garlic, cinnamon, clove, turmeric, amla, basil etc. Their consumption was recommended in various forms like consuming them uncooked, consuming with honey, soaking in water and then consuming or boiling in water for consumption, and even inhaling the fumes after burning or cooking certain agents. These agents have various antimicrobial, antiviral, anti-inflammatory or immune-modulatory roles which might have beneficial effects in preventing or treating COVID-19 infection.

Various governments in different countries have formally and informally recommended use of various herbs and natural agents in the prevention and management of COVID-19 infection. It is seen that there is geographical predilection seen for increased usage of herbs in China; South Asia including India, Bangladesh, Nepal, Afghanistan, and Pakistan; Middle Eastern countries including Saudi Arabia, Egypt, Iran; Africa; Latin America etc. which increased during COVID19 pandemic.

3. Traditional Medicinal Agents in India

The Indian traditional medicine system is one of the oldest systems of medical practice in the world. The Indian Ministry of Health has established six systems of medicine namely the Ayurveda, Yoga, Unani, Siddha, and Homeopathy: AYUSH department that was formed as Ministry of AYUSH in 2014 has also laid down specific COVID-19 prevention and treatment guidelines.⁵ It recommends the use of spices like turmeric, garlic, cumin etc. To drink herbal tea / decoction (kadha) with cinnamon, ginger, black pepper, basil leaves with lemon juice or honey added for better taste. It also recommends the consumption of Golden Milk i.e. half teaspoon turmeric powder added to a glass of hot milk.

Topical application of oils like sesame oil into the nostril is recommended to inhibit the virus attack. The mode of transmission of coronavirus infection is through respiratory tract so the possible mechanism of this topical application is that the viscous nature of the oil makes the flow of the virus typical and the hydrophobicity of the oil prevents the transmission of the virus from nostril to throat and respiratory system.

4. Common Herbs and their Medicinal properties

Some herbal medications or dietary ingredients witnessed increased usage or consumption during COVID pandemic as preventive or therapeutic agents.

4.1. *Neem (Azadirachta indica)*

Neem is a traditionally established medicinal plant having antiseptic, anti-inflammatory, antioxidant, and immune-boosting properties. It is known to have detoxifying properties too. Either it is chewed raw or 4-5 leaves are boiled in water and the strained water is consumed. Pertaining to SARS-Cov-2 virus, its compounds such as nimbolin, nimocin can bind to its envelope, membrane and glycoprotein and exerts its inhibitory role.⁶ In spite of its traditional usage, it is necessary to establish its toxicity profile also as clinical cases of acidosis and renal injury has been also reported.⁷

4.2. *Garlic (Allium sativum)*

Garlic has sulfur containing (allicin and alliin) and non-sulfur containing (flavonoids and saponins) active metabolites. Garlic has its role in COVID management possibly due to its ability to modulate cytokine production (up-regulates T-Helper cells, cytotoxic T cells and NK cells), immunoglobulin production, phagocytosis and activation of macrophage. It is thought to inhibit SARS-CoV-2 by forming hydrogen bonds between amino acids with the binding site of main structural protease of SARS-CoV-2.⁸

4.3. *Ginger (Zingiber officinale)*

Ginger contains about 400 different compounds but pharmacological effects are largely due to its terpene and phenolic compounds which contributes to its anticancer, antioxidant, anti-inflammatory, antiviral, antibacterial, antidiabetic effects. Fresh ginger extracts exerts potent antiviral effects against human respiratory syncytial virus (HRSV) and rhinovirus, by blocking the viral attachment and penetration into host cells. It also inhibits viral replication in the lower parts of respiratory tract by secreting interferon (INF- α and β). Ginger derived phenolic compounds include gingerols which have a high binding affinity to various proteases of SARSCoV-2 necessary for viral replication. Ginger can potentiate antiviral immune responses and exert direct anti-SARS-CoV-2 effects as well as modulate macrophage activation and attenuate the generation of pro-inflammatory mediators.⁹

4.4. *Black cumin seed (Nigella sativa)*

It has been traditionally used as a very common food additive and spice. It has been used for the treatment of fever, chest congestion, cough, bronchitis etc. It has

diverse range of indications in various upper respiratory infections due to its anti-hypersensitivity and anti-inflammatory properties. In the context of COVID infection, its constituent mainly thymoquinone reduces the levels of pro-inflammatory mediators including IL-2, IL-4, IL-6 and IL-12, while enhancing IFN- γ .¹⁰

4.5. *Saffron (Crocus sativus)*

Saffron is the dried red stigma of the flower of the herb *Crocus sativus*. It is considered to be the most valuable spice by weight. It has a varied range of medicinal properties being antihypertensive, antitussive, antioxidant, anti-inflammatory and immune-modulatory. The major compounds responsible for antioxidant and anti-inflammatory role are crocetin esters, picrocrocin and safranal. Various in-vitro and in-silico studies have shown immune-promoting action owing to its activity on Toll-like receptors and inflammatory signaling pathways increasing the levels of IgG.¹¹

4.6. *Indian gooseberry or Amla (Phyllanthus emblica)*

Amla is a rich source of vitamin C which significantly increases the natural killer cell activity and reduces oxidative stress. It has its role as an antioxidant, immune modulatory, anticancer, antimicrobial, cytoprotective, analgesic, antipyretic, anti-diabetic properties.¹² *P. emblica* has immunomodulatory role; it has Ellagic acid which is a very powerful antioxidant, possess potent free radical scavenging agents which has cyto-protective effects.

4.7. *Basil/ Holy basil/ Tulsi (Ocimum sanctum)*

It is an aromatic shrub which has both medicinal as well as spiritual properties. It exhibits a vast array of benefits. Since ages, the dried leaves have been used to repel insects when mixed with stored grains. It exhibits broad spectrum antimicrobial activity, has the ability to counter metabolic stress through normalization of blood glucose, blood pressure and lipid levels; has effects on memory and cognitive function through its anxiolytic and anti-depressant properties. In Ayurveda, it is termed as “elixir of life”.¹³ The various compounds found in *Ocimum* genus like kampferol, quercetin, apigenin, ursolic acid are potential inhibitors of SARS-CoV-2 protease.¹⁴

4.8. *Turmeric (Curcuma longa L.)*

Turmeric is an ancient Indian spice, medicinal herb and a food dye. It has been used in the traditional medicine for a variety of illnesses such as inflammation, infectious diseases, gastric, hepatic and blood disorders. Curcumin is the major polyphenol isolated from the rhizome of turmeric. It has a wide range of pharmacological effects like antioxidant, anti-inflammatory, antimicrobial, antitumor

activities. Curcumin has antiviral properties against human cytomegalovirus (HCMV), Zika virus, Chikungunya virus, Dengue virus, Epstein Barr virus (EBV), Influenza A virus (IAV), Hepatitis virus, Human Immunodeficiency virus (HIV), and even SARS-CoV virus. In silico studies have demonstrated curcumin having potential against the binding proteins of SARS-CoV-2 and its cellular receptors. It also acts by inhibiting the endosomal acidification and processing of the viral proteins necessary for viral release.¹⁵

4.9. Black pepper (*Piper nigrum L.*)

Black pepper is the world's most traded spice. Since ages it is being used as a medicine and as a spice. Its spiciness is due to the alkaloid piperine which possesses a wide range of pharmacological properties like antihypertensive, antidepressant, analgesic, antimicrobial, antioxidant, anti-inflammatory, antiplatelet, antiasthmatic. Piperine is shown to possess immunomodulatory and antiviral properties against SARS-CoV-2 inhibiting the viral replication.¹⁶

4.10. Cinnamon (*Cinnamomum verum or Cinnamomum cassia*)

Cinnamon is a spice obtained from the inner bark of tree species from the genus *Cinnamomum*. It is a very common food condiment and a flavoring additive. It has a role in traditional medicine owing to its role as antimicrobial, antifungal, antiviral, antioxidant, antihypertensive, antidiabetic, immunomodulatory, cardioprotective and nephroprotective effects. It has been used in traditional medicine to treat throat infections, common cold, headache etc. Its pungent taste and the characteristic aromatic scent are due to cinnamaldehyde. It has about 80 aromatic compounds including eugenol. Its role against SARS-CoV-2 is postulated due to its action against viral proliferation by targeting the essential proteins of the virus including SARS-CoV-2 spike protein and SARS-CoV-2 main protease.¹⁷

4.11. Clove (*Syzygium aromaticum*)

Cloves are the aromatic flower buds of a tree in the family Myrtaceae. They are commonly used as a spice, flavoring or fragrance agent in consumer products such as toothpaste, soaps, or cosmetics. Other than their usage in food industry, they have established medicinal properties like antibacterial, antithrombotic, antioxidant, anti-inflammatory and immunostimulatory. Clove essential oils finds its applications in dental care and treatment of gum infections. The phytochemical like eugenol, methyl salicylate and methyl amyl ketone are responsible for the aroma of cloves. Chewing cloves directly or consuming them in a tea is reported to bring relief in sore throat and coughing. When mixed with honey, it eases shortness of breath. They seem to possess antiviral properties owing

to high affinity to the main protease of SARS-CoV-2 acting as its inhibitor. Computational studies suggest that phytocompounds extracted from cloves may act as potent anti-COVID drugs.¹⁸

4.12. Honey

Honey is a mixture of sugars and other carbohydrates mainly fructose and glucose, others being maltose, sucrose and complex carbohydrates. It is a mixture of sugars, amino acids, phenolic compounds, vitamins and minerals. As a folk treatment modality, honey has been used for burns and skin injuries. It also possesses topical antibiotic properties. The World Health organization (WHO) recommends honey as the treatment for cough and sore throats, including for children.¹⁹ Honey has been recommended to handle seasonal allergies. Consumption of warm water with honey on empty stomach early morning acts as a potent cleansing and detoxifying agent. It is postulated that honey can suppress viral growth by inhibiting viral replication because of compounds like ascorbic acid, flavonoids etc. Owing to its antioxidant properties, it has a role as protective agent in patients infected with SARS-CoV-2 tackling cytokine storm that occurs in COVID. Honey also possess immunomodulatory properties, activates immune system, suppress mitogen activated protein kinase (MAPK) and nuclear factor kappa B and various proinflammatory cytokines.²⁰

5. Safety Concerns of Herbal Medications

Recently the World Health Organization (WHO) with African Centre for Disease Control (CDC) constituted a committee to guide the African countries on use of herbal medicines against COVID-19.²¹ However, WHO also cautioned against the use of herbs which have not undergone rigorous clinical trials to ascertain their safety and effectiveness against COVID-19 infection.²² The practice of using traditional methods of handling a disease as grave as COVID-19 infection received negative response from the scientific communities as well. On 14th April 2020, China approved three patent herbal drugs as possible treatment against COVID-19 infection relieving symptoms such as fever, cough, fatigue and reduces the possibility of patients developing severe symptoms.²³ On May 15, 2020 there was a publication in Lancet, cautioning the use of herbal drugs citing the lack of evidence for their efficacy and safety concerns.²⁴ This was followed by a counter explanation and point by point rebuttal of the article advocating the use of herbal products.²⁵ DiPietro and Mondie reviewed the toxicities of various herbal preparations which have been recommended as a part of COVID-19 management in certain countries especially when self-prescribed, misused or prepared by untrained personnel.²⁶

The valid concerns related to the use of herbal agents are issues related to quality control, unethical production practice, and inadequate information about the composition, use and mechanism, lack of well-established regulatory bodies, inadequate information about herb-drug interaction and possible overuse or abuse. In current times, the growing interest in allied and alternative therapy modalities have led to increased research and validation of various herbal and traditional medicinal agents supported with evidence backed results. Further researches are required to further support the validity of this alternate modality of management of various diseases.

6. Discussion

Ayurveda is the system of medicine that evolved in India dating back to the Vedic era. The current allopathic system of medicine is evidence based and is supported with multi-level laboratory and subject-based drug trials; but there is no denial that the age old traditional medicines and alternative therapy methods like Ayurveda, Yoga, Unani, Homeopathy and naturopathy have been carried forward over centuries and still find its place in managing chronic conditions where the current allopathic treatment modalities fail. They lack the enormous scientific data, peer reviewed clinical trials or animal studies, safety and efficacy data as compared to the current pharmaceutical agents; but the fact that they have been in use since ages, providing beneficial results to billions of people; can also be not refuted.

Whenever the current science failed, people turned towards alternative medicine. Though diseases like cancer still do not have any definitive treatment but we are better equipped with its early detection, diagnosis and better management now as we were few decades ago that has helped increasing the longevity and reducing the mortality of the effected patients. Back then, people switched to alternative treatment options like Yoga which promised excellent results. In the absence of any definitive treatment, there was no option but trying. It has been now scientifically proven that yoga interventions are beneficial in improving the adverse symptoms in cancer patients, either caused by the disease itself or its treatment.²⁷ Yoga has been now included as a part of Integrative oncology where complementary and alternative medicine treatment modalities are being integrated with the Conventional Cancer management programs. Yoga is now accepted world over as a very effective way of improving the overall well-being of a person improving the physical and psychological being of an individual, improving the immunity, reducing the severity of infection and inflammation, improving the respiratory function and the quality of life.²⁸

Since the onset of this pandemic, various researches have been conducted and trials are going on wherein these alternative treatment modalities are being tested as adjuvant therapy options along with various pharmacological agents.

Traditional Chinese medicines have shown encouraging results in improving the clinical symptoms, reducing mortality and reducing the recurrence of SARS-Cov-2 virus.²⁹ Therapies using plant extract have been successful in managing respiratory symptoms and reducing the level of biomarkers of inflammation. Many herbs have immunomodulatory properties that can be used to strengthen the immunity and protect the body against COVID-19 infections.³⁰

A systematic review and meta-analysis of randomized controlled trials studying the use of herbal medicines for the treatment of COVID-19 showed that the combined therapy of herbal medicines with Western medicines had significant beneficial effects than the use of allopathic medication alone.³¹ A web-based cross-sectional survey showed that about 80% respondents used medicinal plants as preventive agents against COVID-19 infection and 71% used them (eucalyptus, ginger, chamomile) for treating respiratory symptoms.³² A case of COVID-19 positive patient residing in New York being treated entirely with Ayurveda was also reported to encourage more studies in this direction.³³

The whole world came to a standstill in 2019 when this pandemic hit the humanity. The advances in science has led us to the situation where the nature of infection and the causative agent was deciphered within a month's time and in record time the vaccine against COVID-19 was generated. But still it led to an enormous loss of mankind both psychologically and physically. In spite of this enormous loss, those who have survived this infection, are still battling with various after effects of the infection which range from fatigue, headache, anosmia, neurological complaints (depression, anxiety, attention disorder), hair loss, dyspnea, cough, hearing loss or tinnitus, vertigo, increased resting heart rate, arthralgia, reduced pulmonary capacity etc.³⁴

7. Conclusion

The role of Ayurveda or various herbal agents as medicinal agents in the prevention or cure of various ailments or medical conditions cannot be overlooked. It is an established system of medicine since ages. We may not have the scientifically backed evidence of each and every agent, but we have the technology where the use of such agents can be validated by laboratory testing and experimentation.

The administration of vaccines has placed us in a much better position now but still, there is no definitive treatment of this infection. We are relying upon the preventive aspect of the infection which involves masking, social distancing, hand sanitation and vaccines; but once a person gets infected, the treatment is symptomatic. In such a situation the use of allied sciences like yoga, meditation or various herbal and ayurvedic agents which help in boosting the immunity may play a very vital role. Once a person gets infected, such modalities may then play an important role in palliative care and hastening the recovery.

As with any pharmacological agent, these herbal agents may also have certain limitations. The need of the hour is designing more researches and well-designed drug trials, so that their beneficial effects may be utilized along with the knowledge about their side effects or effects due to overuse or abuse after indiscriminate usage. What we require is subject oriented researches so that the already known fact about their importance may be backed with scientific evidence, and we can avail the benefits of these agents better with minimal side effects.

8. Source of Funding

None.

9. Conflict of Interest

None.

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