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Review Article

SAUSSUREA COSTUS AS HERBAL MEDICINES HAVE IMMUNOMODULATORY AND POTENTIAL NUTRACEUTICAL COMPONENTS THAT MAY HELP IN COVID-19 REMEDY

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Abstract

The epidemic associated with the severe acute respiratory syndrome is Corona Viral Disease-2019 (COVID-19) induced thousands of fatalities around the world. The infection was initially identified in Wuhan (China) in late December 2019, introduced from zoonotic source. Coronavirus 2 (SARS-CoV-2) is the extension of severe acute respiratory syndrome and found to have 96% of its genomic similarity with the bat coronavirus. SARS-CoV-2. That is a single-stranded positive RNA sense virus with a size of 29.7 kb. That also resemble with the sequence of the Nidovirales, family Coronaviridae, and genus Coronavirus. This kind of RNA encodes two huge non-structural polyproteins and four main structural proteins. The timely introduction of vaccines and antiviral therapies have controlled the fatalities of this mortal disease. Moreover, the Terpenes included in *Saussurea* can assist in relieving pain and inflammation. *Saussurea costus* (*S. Costus*) has been demonstrated to have anti-inflammatory, antiulcer, anticancer, and hepatoprotective effects *in vitro* and *in vivo* experiments. This plant's sesquiterpene lactones, Costunolide, dehydrocostus lactone, and cynaropicrin have all been identified and proven to have therapeutic promise. So, in this review article we have described the plant that may help to treat the COVID-19. *S. Costus* is a crucial plant with medicinal significance, the roots which are utilized for healing justifications all over the history of mankind's giant safety and usefulness. The outputs of other studies showed the existence of several bioactive substances phytochemical molecules that has antiseptic, antibacterial, antifungal, antiviral, anti-inflammatory, antioxidant, anti-lipid peroxidation, immunostimulant, analgesic, bronchodilator, hepatic-protective, and anti-hepatotoxic properties. *S. Costus* has immunomodulatory properties on cytokine delivery and has complement-inhibitor substances useful in the cure of a few disorders linked to marked stimulation of the complement system, as in breathing problems.

Keywords: Saussurea costus, COVID-19, Pandemic, Respiratory distress, Medical plants, Herbal medicine.

Author contributions:

This work was carried out in collaboration among all authors. **Marwa M. Elmaghrabi**, designed the study of proposed hypothesis **Najwa M. Majrashi**, **Marwa M. Elmaghrabi** and **Dalal S. Alharbi**, compile the scientific contents. **Najat. A. Marraiki** and **Taha Nazir**, elaborated study to make it more credible. Whereas, **Umer Farooq** and **Ishtiaq Rabi** managed the literature searches and citation part of the manuscript. Thus, all authors have read and approved the final manuscript for publication in this journal

Introduction

COVID-19 is a viral infectious disease with the severe acute respiratory syndrome, initially identified and discovered in December 2019 in Wuhan City, Hubei Province, China [1]. The SARS-CoV-2 or COVID-19 spread promptly to all 34 provinces and major cities in China. Afterward, infection diagnosed and recorded in 144 countries covering all 5 continents a per report of World Health Organization, 2020. SARS-CoV-2 is the member of Coronaviridae family's Nidovirales order. It is single (+) stranded RNA with symmetric helical nucleocapsids [2]. The virus encodes twenty proteins, including four major structural proteins S – spike, E – envelope, M – membrane and N – nucleocapsid. There are several nonstructural proteins including coronavirus main protease (3CLpro), RNA dependent RNA polymerase (RdRp) and papain-like protease (PLpro) [3]. The virus attack on the angiotensin-converting enzyme II (ACE2) receptor and enter into the alveolar cells. Then hurt the vital pulmonary functionality and respiratory system. The receptor for SARS-CoV-2 permit to human and bat cells. SARS-CoV-2 connects with the host cells through interaction with spike protein's receptor binding motif of the receptor-binding domain or RBD. The C-terminal S2 subunit of the spike protein will undergo conformational modifications as a result of this interaction (which is important for virus-cell membrane fusion) [4]. The complex S protein ACE2 is then proteolytically processed by the host cell-t transmembrane serine protease TMPRSS2, resulting in ACE2 cleavage and hence viral entry into the host cell. The double membrane vesicle is formed as a result of the nonstructural proteins causing cellular membrane rearrangement. Conversely, the genomic RNA is translated into subgenomic RNA, resulting in the creation of structural (spike, envelope, membrane, and nucleocapsid) and auxiliary proteins. Finally, before being released into the secretory pathway, virions are produced in the ER-Golgi intermediate complex [5].

Overview of medical plants

Humans have used medicinal plants since ancient times for various purposes. It found many pieces of evidence that indicate this, including records of Mesopotamia, Egypt, Greek, and Islamic civilizations. Sumerian clay slab from Nagpur, which is approximately 5000 years old. *Cedrus Duham.* species, *Commiphora myrrha* Engl., *Cupressus sempervirens* L., *Glycyrrhiza glabra* L., and *Papaver somniferum* L. are among the plants mentioned in the oldest documents. These medicines were first utilized in their most basic forms, including powders, teas, tinctures, and poultices. The separation of active components from medicinal plants was done in the early nineteenth century. Many therapeutic qualities of a single plant are observed in phytomedicine since it contains many phytochemicals. Overall, these phytochemicals can be classified as having 1) antiviral, 2) anti-inflammatory, 3) immunomodulatory, and 4) other properties [6]. Antiviral plants like *Sambucus nigra*, *S. costus*, *Withania somnifera*, *Silybum marianum*, and *moringa oleifera* have been used to treat human viruses like influenza, human immunodeficiency virus (HIV), Hepatitis C virus, and Herpes simplex. The twenty-seven were investigated as medicinal plants from southern Nigeria for their effectiveness against positive-stranded RNA viruses like enteroviruses and found that they had substantial antiviral activity [7]. The complexity of plants' secondary metabolism is responsible for their various therapeutic properties. Although herbal medicine is simple to use as a whole plant crude extract, decoction, or tea, the efficacy of plant-based chemical components can only be reached when they are taken in their purest form or in combination to generate a com-

pound medicament. Numerous plant-derived chemical compounds have been shown to be efficient antiviral medicines. Hundreds of different chemicals have been demonstrated to be effective against human viruses in terms of direct antiviral action or symptom relief in studies [8].

In general, phytochemicals suppress viral replication, stop transcription, and production of viral proteins by interfering with viral entrance via attachment to viral proteins, inhibiting viral replication, stopping transcription, and expression of viral proteins.

Medical plants with Pharmaco-Therapeutical effects against COVID and SARS

Medical plants contain a high concentration of viral protein inhibitors that can be utilized to treat SARS. Medical plants can produce metabolites that impede the activity of enzymes, proteins, and viral propagation. Certain traditional herbal treatments protected healthy people from SARS-COV2 infection and improved the health of patients with mild to severe symptoms [9].

Because most of the active proteins in the SARS-COV2 infection cycle are conserved, it is envisaged that the results of previous coronavirus generations, notably SARS-COV2, would be relevant to the new coronavirus. Figure 1 depicts possible plant-based antiviral approaches for emerging coronaviruses.

Plant immunology is a complicated system that employs a variety of tools to recognize and eliminate invading pathogens, such as cell surface and intracellular receptor proteins. Plant lectins are carbohydrate-binding proteins found in a variety of plants, including tobacco, soy, and leeks, that can act as immunologic receptors and defense proteins. One of the plant-based chemicals that could be addressed as a therapy for COVID-19 is plant lectins. Several investigations have discovered that a number of plant substances can suppress SARS-COV's proliferation trend [10].

Secondary Metabolites of the Medicinal Plants

Secondary metabolites are non-essential molecules for plant cell survival. In response to biotic and abiotic stressors, such metabolites are produced [11]. When stress appears, the expression of secondary metabolites increases. Trashinones, Flavonoids, Carotenoids, and Diarylheptanoids are examples of active chemicals

found in plants. A variety of plant secondary metabolites has been studied for their capacity to inhibit SARS-COV and have been discovered to have powerful antiviral and anti-SARS-COV effects. Some well-known examples of such compounds are:

Glycyrrhizin

Glycyrrhizin is the active element in licorice (*Glycyrrhiza glabra*). For ages, this chemical has been used to treat gastritis, bronchitis, and jaundice, and it has been demonstrated to have antioxidant and anti-inflammatory qualities, as well as the capacity to boost interferon production in the. Glycyrrhizin has been demonstrated to inhibit SARS-COV agent adhesion to cells, particularly during the early phases of the viral infection cycle revealed that Glycyrrhizin, a compound composed of flavonoids, Glycyrrhetic acid, Sitosterol, and hydroxyl coumarins, had potent anti-SARS-COV activity [12].

Baicalin

Baicalin is a significant component of plants in the *Scutellaria* genus and is responsible for the therapeutic properties of *Scutellaria baicalensis*. This flavone glucuronide has been demonstrated to have anti-apoptotic and antioxidant properties and has previously been used to treat pulmonary arterial hypertension revealed that this medication has anti-SARS-COV action in vitro, with a greater inhibitory impact than Glycyrrhizin, Interferon-alpha, and Interferon-beta 1a and a substantially lower toxicity concentration for the cell lines [13]. The antiviral action of this molecule was judged so important that a patent for anti-SARS pharmaceutical production employing this biochemical compound was later awarded [14]. The extract flavonoids from *Scutellaria baicalensis* demonstrated substantial antiviral agent on

Lipopolysaccharide-activated cells in vitro, and oral treatment of the substance dramatically enhanced the survival rate of influenza Virus-infected mice.

Furthermore, the in-vivo discovery validated Baicalin's antiviral activity in the in-vivo setting. However, no in-vivo study on the impact of Baicalin on SARS-COV-infected model animals has been discovered. Baicalin was discovered to have a positive tendency to inhibit Angiotensin-converting enzyme 2 in a computer simulation of the compound action in the instance of COVID-19 illness (ACE2). A recent study found that an extract of *Scutellaria baicalensis* might lower the 3CLPro activity of the new SARS-Cov2 virus in vitro, indicating that this chemical has potential for further investigation in COVID-19 illness [15].

Quercetin

Organosulfur compounds are abundant in plants of the *Allium* genus, including onions (e.g., *Allium cepa*), garlic (e.g., *Allium sativum*), and leeks (e.g., *Allium sativum*) (*Allium porrum*). Organosulfur compounds are organic macromolecules that contain sulfur in their biological structure. Organosulfur compounds from *A. porrum* were revealed to have significant capacity in inhibiting Human ACE2 enzymes and hence have the potential to disrupt SARS-attachment COV2's to the cells in a recent in-silico analysis for SARS-COV2 [16].

Quercetin is a flavonoid that has been identified in abundance in onion and garlic species, as well as in sulfonic substituents (albeit in fewer amounts) demonstrated that quercetin-3-galactoside inhibited the 3CLPro of SARS-COV. In-vitro suppression of SARS-COV 3CLPro by Quercetin and Quercetin-3-galactoside was verified in subsequent experiments [29]. It was also discovered that quercetin 3Dglucoside has the capacity to block the MERS-COV 3CLPro. This chemical has been discovered to have little toxicity to cells in vitro, and it is one of the key natural components being studied for the treatment of COVID-19 illness [17].

Saussurea costus

S. costus related to the family Asteraceae, worldwide distributed however, many species are distributed in Pakistan and India. The plant has been well-known for more than 2500 years. It was used by the ancients in the medical field. The biological functions of the roots of *S. costus* were widely investigated by much scientific literature. Numerous compounds from the plant which has nutraceutical compounds including anthraquinones, flavonoids, alkaloids, and terpenes [18]. Terpenes have anti-inflammatory and antitumor compounds, such as costunolide, dihydrocostunolide, 12 methoxydihydrocostunolide, dehydrocostus lactone, α -hydroxy dehydrocostus lactone, β -hydroxydehydrocostus lactone, lappadilactone, betulinic acid, betulinic acid methyl ester, mokko lactone, reynosin, Santamarina, cynaropicrin, saussureamines A-C, alantolactone, isalantolactone, α -cyclocostunolide β cyclocostunolide, isodihydrocostunolide, 1beta-Hydroxy arbusculin A arbusculin B6. Additionally, it contains pregnenolone, β -sitosterol, daucosterol, 12-octadecadienoic acid, costic acid, myrcene, p-cymene, tannin, caryophyllene-oxide, octanoic acid, stigmasterol, lupeol, botulin, caryophyllene, palmitic acid, oleic acid, inulin, camphene, alpha phellandrene, hexanoic acid, saussurine, acetic acid, beta-ionone, friedelin, taraxasterol, plus many other ingredients.

S. costus has numerous pharmaceutical properties as antiseptic, antibacterial (costic acid, dehydrocostus lactone, myrcene, p-cymene, tannin15), antifungal (caryophyllene oxide, myrcene, octanoic acid, p-cymene15), antiviral (p-cymene, stigmasterol, tannin15), antitumor (lupeol, p-cymene15), anti-Epstein-barr virus (lupeol, betulin15), antinematodal anthelmintic (tannin15), anti-trypanosome 6, anti-malarial, (lupeol15), anti-leishmanic (caryophyllene15), anti-inflammatory, antioxidant (myrcene, palmitic acid, stigmasterol, tannin15), anti-lipid peroxidation37, anti-leukotriene-D4 (oleic acid15), immunostimulant (inulin15), immunomodulating, analgesic (myrcene, p-cymene15), antipyretic (beta-

sitosterol15), bronchodilating16 (caryophyllene15), expectorant (camphene, inulin, alpha phellandrene, caryophyllene, hexanoic acid15), gastric cytoprotective (caryophyllene15), antiulcer (tannin15), choleric (oleic acid15), cholagogic, carminative, antispasmodic, (myrcene,saussurine15), antidiarrheal (tannin15), antibacillary (p-cymene, acetic acid, alpha-phellandrene, beta-ionone, beta-sitosterol, caryophyllene15) astringent16, hepatoprotective (tannin, pcymene15), antihepatotoxic (tannin15), hypoglycaemic (inulin15), antihyperglycemic (lupeol15), hypolipidemic50 (beta-sitosterol15), hypocholesterolemic (inulin, oleic acid, stigmasterol, beta-sitosterol15), angiotensin converting enzyme (ACE) inhibitor (myrcene15), diuretic (friedelin15), anti-edema (caryophyllene oxide, lupeol, taraxasterol15), anti-rheumatic (lupeol15), anti-dermatitis (caryophyllene15), anticancer. (caryophyllene oxide, caryophyllene, costunolide, lupeol, tannin, betulin15), sedating, and anticonvulsant properties (myrcene15) [19].

S. costus is used to cure diabetes mellitus, bacterial infections tuberculosis, leprosy fever, headache, pain, cough, bronchial asthma, diarrhea, cholera vomiting, dyspepsia typhoid, hiccups, gastric ulcer, abdominal pain diarrhea tenesmus arthritis rheumatoid arthritis, systemic lupus erythematosus, respiratory distress, chronic skin diseases ringworm and scabies [20].

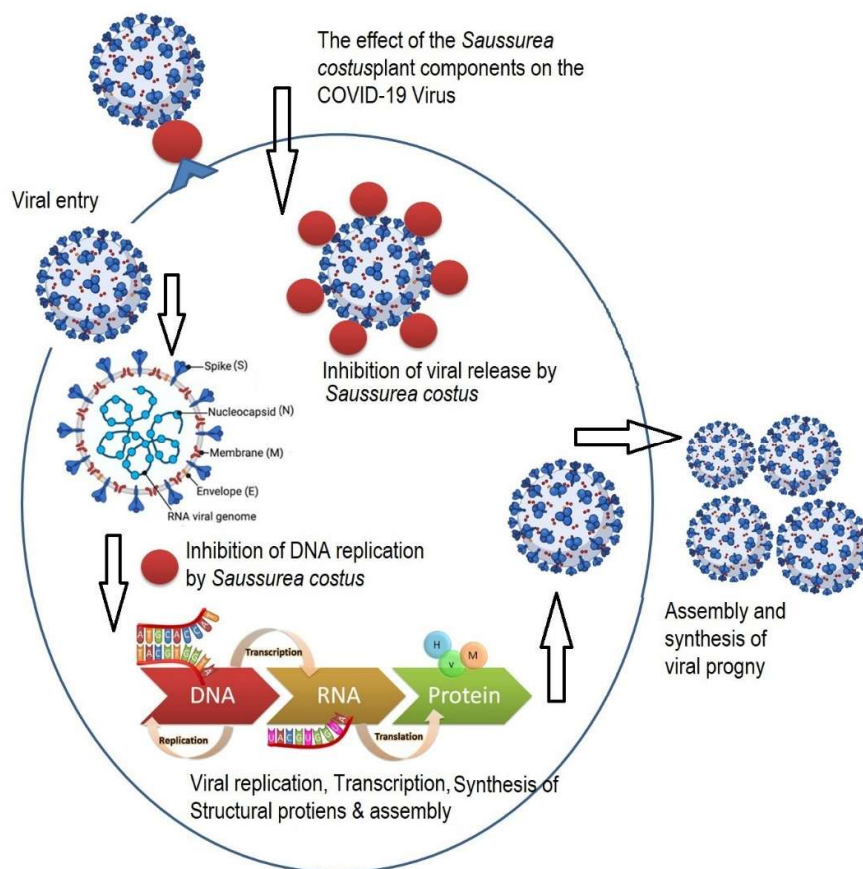


Figure1: Replication cycle of COVID-19 in the human body and the intervention of phytomedicine against Coronaviruses.

Table 1. Some medical plants with the potential of the anti SARS-COV activity, their inhibition, and its effective composition

a-Angiotensin-converting enzyme II (ACE2)

b-chymotrypsin-like protease (3CLPro)

Family	Plant name	Inhibition way	Effective composition	Ref
Amaryllidaceae	<i>Allium sativum</i> (Garlic)	ACE2 receptor inhibitor ^a	Allyl disulfide	[16]
Anacardiaceae	<i>Galla chinensis</i> (Nutmeg tree)	Viral spike protein and human ACE2 receptors inhibitor	Tetra-O-galloylβ-d-glucose	[33]
Apiaceae	<i>Angelica keiskei</i> (Ashitaba)	3CLpro Inhibitor ^b	Chalcones	[21]
Betulaceae	<i>Betula pubescens</i> (Downy birch)	3CLpro Inhibitor	Betulinic acid	[22]
Brassicaceae	<i>Isatis indigotica</i>	3CLpro Inhibitor	Hesperetin/ Sinigrin	[23]
Celastraceae	<i>Tritergium regelii</i> (Regel's threewingnut)	3CLpro Inhibitor	Celastrol/Pristimerin Tingenone/ Iguesterin	[24]
Cephalotaxaceae	<i>T. nucifera</i> (Japanese nutmeg-yew)	3CLpro Inhibitor	Plant extract	[25]
Crassulaceae	<i>Rhodiola kirilowii</i>	Viral growth inhibitor	Luteolin	[33]
Cupressaceae	<i>Chamaecyparis obtusavar formosana</i>	3CLpro Inhibitor	Savinin - Hinokinin-Betulonic acid	[22]
Polygonaceae	<i>Reynoutria</i> (Multiflora Tuber)	Viral spike protein and human ACE2 receptors inhibitor	Emodin	[26]
Santalales	<i>Cibotii</i> (Showy mistletoes)	3CLpro Inhibitor	Plant extract	[27]
Sapindaceae	<i>Litchi chinensis</i> (Lichi)	3CLpro Inhibitor	Flavonoids extract	[28]
Saururaceae	<i>Houttuynia cordata</i> (Fish mint)	3CLpro Inhibitor	Plant extract	[29]
Solanaceae	<i>Nicotiana benthamiana</i> (Benth)	Viral growth inhibitor	NICTABA Lectin	[30]
Theaceae	<i>Camellia sinensis</i> (Black tea)	3CLpro Inhibitor	Tannic acid	[31]
Urticaceae	<i>Urtica dioica</i> (Stinging nettle)	Viral spike protein inhibitor	Urtica dioica agglutinin	[32]
Zingiberaceae	<i>Curcuma longa</i> Isatis	3CLpro Inhibitor	Curcumin	[33]

Immunomodulatory effect of *S. costus*

S. costus was discovered to be the most efficient for obese diabetes when a comprehensive survey and clinical study are conducted on potent hypoglycemic plants of different places from India. Costunolide repressed the assassination activity of cytotoxic T lymphocytes (CTL) by stopping the elevated tyrosine phosphorylation in reaction to the cross-linking of T-cell receptors. Dehydrocostus lactone along with other guaianolides additionally reveal inhibitory activity regarding the killing function of CTL and the induction of intercellular adherence molecule-1 (ICAM-1) [34].

Anti-inflammatory effect of *S. Costus*

S. costus ethanolic extractor revealed anti-inflammatory activities by carrageenan-influenced paw edema and intra-abdominal infection or intra-abdominal sepsis animal models. Costunolide additionally demonstrated an anti-inflammatory effect by disturbing the protein and mRNA expression of interleukin-1b hindering the AP-1 transcription activity [35, 37].

Saussurea contains terpenes, which can help to reduce pain and inflammation. Many botanical remedies have been listed in traditional medical systems such as Chinese, Japanese Kampo, and Indian Ayurveda, all of which claim to alter the immune system's cellular and humoral functioning. Rasayanas are a unique class of immunomodulatory botanicals recognized by Ayurveda [36]. The Rasayana herbs have been discovered to provide a range of benefits, including delaying the onset of senescence and increasing mental functioning by strengthening the psycho-neuro-immune axis. Herbal drugs have been discovered to affect cytokine production, histamine release, immunoglobulin secretion, class switching, cellular receptor expression, lymphocyte expression, and phagocytosis. Phytochemicals produced by botanicals include isoflavonoids, indoles, phytosterols, polysaccharides, sesquiterpenes, alkaloids, glucans, and tannins, and different botanicals from these Ayurvedic classics have been studied for their immunomodulatory properties. *Saussurea lappa*, known as costus, kuth, kushta, kust, muxing, patchak, and Quang Mu Xiang, is a valuable medicinal plant used in Chinese medicine to treat a variety of maladies including asthma, inflammatory diseases, ulcers, and stomach problems. Anti-inflammatory, anti-ulcer, anticancer, and hepatic-protective properties of *Saussurea costus* have been successfully established in a range of *in vitro* and *in vivo* situations. The primary phytoconstituents of this plant have been identified as sesquiterpene lactones, Costunolide, dehydrocostus lactone, and cynaropicrin, all of which have been isolated and shown to have the bioactive potential [37].

Therapeutical effects of *S. Costus* against COVID-19

S. costus by its myrcene ingredient that has an effect on ACE receptors¹⁵, could make the viral entrance more difficult into the cells. *S. costus* is used in the treatment of headache, fever, cough, and bronchial asthma. Oleic acid acts as an anti-leukotriene-D415, as a result, acts as a bronchodilator. *S. costus* is traditionally used as a bronchodilator and as an analgesic, Myrcene and p-cymene have analgesic properties, while camphene, inulin, alpha-phellandrene, caryophyllene, and the hexanoic acid act as expectorant¹⁵. *S. costus* has antimicrobial and antibacterial properties (caustic acid, dehydrocostus lactone, myrcene, p-cymene, tannin¹⁵). It is traditionally used as an antiseptic and possesses antibacterial action against a wide range of human diseases. It exhibited a substantial amount of antibacterial activity against many Gram-positive and Gram-negative pathogenic bacteria, including staphylococcus aureus, pseudomonas aeruginosa, acinetobacter baumannii, escherichia coli, and klebsiella pneumonia. It also has antifungal activity (caryophyllene oxide, myrcene, octanoic acid, p-cymene¹⁵). The decoction of the plant accelerates the endogenous motilin release plus the acceleration of gastric emptying and improves gastric cytoprotection. It boosted mucus discharge and was proved to be an antiulcer agent. Caryophyllene¹⁵ and increased intracellular glutathione are responsible for protection against gastric cell injury. Besides, *S. costus* showed the ability to inhibit several strains of helicobacter pylori¹¹ and it is carminative. Oleic acid has a choleric effect and costunolide has a sialagogic effect. *S. costus* has significant antidiarrheal activity (tannin¹⁵), antiseptic, and astringent agents [14]. It is widely utilized in different medical systems worldwide for the cure of a variety of ailments such as dyspepsia, vomiting, inflammation, diarrhea, tenesmus, and abdominal pain. *S. costus* roots have hepatoprotective properties (tannin, p-cymene¹⁵) and antihepatotoxic effects (tannin¹⁵) [18]. *S. costus* roots have antiviral activity. The studies that demonstrated its antiviral activity were performed on the hepatitis B virus (HBV) and demonstrated its significant activity against the virus and its ability to inhibit hepatitis B surface antigen (HBsAg) expression. Costunolide and dehydrocostus lactone showed that it had

an inhibiting effect on the expression of HBsAg by Hep3B cells. They suppressed HBsAg gene expression at the mRNA level. Costunolide and dehydrocostus lactone are candidates to be developed as potent anti-HBV drugs. P-cymene, stigmasterol, tannin, lupeol, and botulin have antiviral effects. *S. costus* has anti-inflammatory activity. It is frequently used for inflammatory diseases. It inhibited the cytokine-induced neutrophil chemotactic factor induction. Costunolide has anti-inflammatory activity. *S. costus* reduces inflammation and pain by inhibition of the cyclooxygenase (COX) enzyme [12]. *S. costus* is used to treat chronic inflammation of the lungs, chest congestion, lung inflammation, and respiratory distress. Chlorogenic acid in the roots of *S. costus* exhibited antioxidant activity. Myrcene, palmitic acid, stigmasterol, and tannin have antioxidant properties. *S. costus* extract caused dose-dependent protection against lipid peroxidation. *S. costus* possesses immune-stimulant effect (tannin15). It increased the leukocytic count, phagocytosis, and antibody-secreting cells. It inhibited the oxidation of reduced glutathione (GSH) in a dose-dependent manner. The significance of thiols, especially those of cysteine and glutathione, for lymphocyte function, has been known for a long time. GSH is a non-enzymatic mode of defense against free radicals. Glutathione is an important constituent of intracellular protective mechanisms against several noxious stimuli, including oxidative stress. *S. costus* roots have immunomodulatory activity. Cynaropicrin has immunomodulatory effects on cytokine release. *S. costus* has a substance known as a complement inhibitor that is beneficial in the treatment of some disorders linked to stimulating the complement cascade, like systemic lupus erythematosus, respiratory distress, and rheumatoid arthritis. Its roots are used to treat a variety of rheumatic diseases. Lupeol has an antirheumatic effect. *S. costus* has hypoglycaemic activity (inulin15), and it was found to be effective for obese diabetic patients. It showed a significant hypolipidaemic effect in rabbits. Reductions in serum triglycerides and cholesterol were also found to be significant. Beta-sitosterol has hypolipidemic and hypocholesterolemic effects. Inulin, oleic acid, and stigmasterol have hypocholesterolemic effects. *S. costus* roots have spasmolytic activity. Myrcene and saussurine have antispasmodic actions. *S. costus* is known to suppress contractions in the guinea-pig aorta. Sesquiterpenes are renowned for their ability to stimulate the soluble guanylyl cyclase (sGC) which stimulates extrusion of K⁺ ions as a result of which intrinsic Ca⁺⁺ ions via the activation of protein kinase G (PKG) pathway and cyclic guanosine monophosphate (cGMP), resulting in relaxation of smooth muscles [15].

Perspective Developing of Herbal Medicine against CORVID 19

Herbal treatments can effectively treat symptoms like fever, cough, and fatigue, as well as reduce the probability of patients contracting serious infections; nevertheless, while employing previously utilized herbal remedies to treat COVID-19 disease, we must:

First, safety is the most crucial consideration. While proponents argue that herbal therapies are extensively used and safe, the truth is that all drugs have risks. Although these herbal drugs have been used therapeutically for many years, their safety should be carefully evaluated when used to treat a specific sickness such as COVID-19, particularly when paired with other antivirals, antibiotics, and immune suppressants [38].

Second, additional evidence from controlled clinical trials is required to establish the efficacy of these herbal treatments. Because the herbal pharmaceuticals are manufactured prior to any therapy and their composition is predetermined, clinical endpoints such as mortality, time to clinical improvement, and the number of days in an intensive care unit may be used to assess the efficacy of the herbal pharmaceuticals for Covid-19.

Third, the underlying molecular process is unknown. Herbal medications often include a large number of active chemicals, and it is critical to understand which ones are useful and how they operate [39].

Fourth, it should purchase herbal drugs with a doctor's prescription.

Finally, governments have committed vast quantities of money to support the modernization and standardization of traditional medicine, as well as the conduct of long-term basic and clinical research.

Dose and Protocol of *Saussurea costus*

Saussurea is generally sold as a powder, capsules, or the whole root in dried form. It's also available as a liquid, either as an extract or a tincture, which indicates that it's based on alcohol. Many multi-ingredient formulations contain *Saussurea*, including Mu Xiang Shu Qi Wan pills, which are utilized in traditional Chinese medicine [40]. There are no dose recommendations for *Saussurea*. In the single human study of the supplement, children were administered 40 milligrams (mg) of *S. lappa* per kilogram of body weight each day, with no harmful side effects. For a 150-pound adult, that equates to around 2,700 milligrams each day. Because *Saussurea* powders and solutions are frequently combined with water or juice, they should be measured carefully using a measuring spoon or dropper. *Saussurea* root teas and decoctions are popular, but there's no way of knowing how much you're getting from them. Aromatherapy, fragrances, incense, and scented candles all employ *Saussurea* essential oil, which is extracted from the plant's roots. There is no way to determine for sure whether *Saussurea* supplements are genuine or pure because they are rarely subjected to quality testing (until now not approved by the FDA) [41].

According to *S. costus* safety and undesirable effects, there is not plenty of data available. In general, and based on previous studies' output, *S. costus* root may be safe when taken orally. But *S. costus* may contain an impurity called aristolochic acid, which may have carcinogenic and nephrotoxic effects.

In pregnancy and breastfeeding, the safety of *S. costus* has not been detected until now. It was found that *Saussurea costus* may elicit allergic reactions in patients who are allergic to *Saussurea* species and their ingredients, which include the sesquiterpene lactones (STL). Those patients were exposed previously in another study to STLs and were observed they have dermatitis. Concerns have been expressed about the situation of genotoxic embryotoxic of the chemicals' potential. It was found that STLs have a mutagenic effect, and it was documented by Vivo and Vitro assays [42].

Conclusion

Herbal Medicines provide human beings with crucial compounds that may be used to cure different illnesses. Although modern medicine includes procedures that aren't normally considered part of conventional care. Natural therapies will be used as a co-treatment with standard treatments, with the assumption that natural therapies will have no side effects and, in the quest, to do more to alleviate one's symptoms and enhance the well-being.

Recommendation

Research centers and organizations must focus more on herbal medicines in parallel to chemical drugs and evaluate of the nutraceutical potential of *S. costus* as the extraction of bioactive substances from the roots of *S. costus* is the best way to get new natural and effective nutraceutical compounds as natural therapies. In the case of COVID-19, *S. costus* may be used as a recommended natural therapy, and patients should be informed, and to be demanded to take part in the clinical trials and share their data and illness history, and signed the consents before using their data in research.

The Additional researches are required to quantify the effectiveness of *S. costus* for its use in the COVID-19 remedy.

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