Sohag University Sohag Medical Journal Faculty of Medicine

Saussurea costus may help in the treatment of COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19) is an emerging disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causing an ongoing pandemic and is considered as a national public health emergency. The signs and symptoms of COVID-19 vary from mild symptoms to a fulminating disease with acute respiratory distress syndrome (ARDS) and multi-organ failure, which may culminate into death with no available vaccines or specific antiviral treatments. God provides us with important medicinal plants. Here I shall shed the light on one of these plants that may help in the treatment of COVID-19 or may even cure it. *Saussurea costus* (*S. costus*) is a popular plant with medical importance, the roots of which are widely used for healing purposes throughout human history with great safety and effectiveness. Previous studies revealed the presence of many bioactive phytochemical molecules that has antiseptic, antibacterial, antifungal, antiviral, anti-inflammatory, antioxidant, anti-lipid peroxidation, immunostimulant, immunomodulating, analgesic, bronchodilor, hepatoprotective and antihepatotoxic properties. *S. Costus* has immunomodulatory effects on cytokine release and has complement-inhibitor substances helpful in the treatment of some diseases related to marked activation of the complement system, like respiratory distress.

Keywords: *Saussurea costus*, COVID-19, respiratory distress.

Background:

S. costus (synonymous with *Saussurea lappa*), belongs to family Asteraceae, widely distributed in different regions in the world; however, numerous species are found in India[1], in Pakistan, and some parts of Himalayas[2]. The plant is well-known about 2500 years ago. It is used in different ancient systems of medicine such as Ayurveda, Unani, and Siddha[3]. *S. costus* is well Known in Islamic medicine, which enlisted in the Holy Ahadith said by Prophet Muhammad (Peace be upon him). It is known in Arab countries as Al-Kost Al-Hindi[4], Al-Kust, and Al-Qust[5], and used by traditional healers since the era of Islamic civilization[4].

In scientific literature, the biological activities of the roots of *S. costus* are widely investigated[6]. Various compounds isolated from the plant have medicinal properties including terpenes, alkaloids, anthraquinones, and favonoids. The plant has many terpenes with anti-inflammatory and antitumor properties, such as costunolide, dihydrocostunolide, 12-methoxydihydrocostunolide, dehydrocostus lactone, dihydrocostus lactone[7],α-hydroxydehydrocostus lactone, β-hydroxydehydrocostus lactone, lappadilactone[8], betulinic acid, betulinic acid methyl ester, mokko lactone[9], reynosin, santamarine, cynar-opicrin[10], saussureamines A-C[11], alantolactone, isoalantolactone, α-cycloco-stunolide[12], β-cyclocostunolide, isodihydrocostunolide[13], 1β-hydroxy arbusculin A[9], arbusculin B[6]. Also, it contains

pregnenolone, β-sitosterol, daucosterol, 12-octadecadienoic acid[14], costic acid, myrcene, p-cymene, tannin, caryophyllene-oxide, octanoic acid, stigmasterol, lupeol,botulin, caryophyllene, palmitic acid, oleic acid, inulin, camphene, alphaphellandrene, hexanoic acid, saussurine, acetic acid, beta-ionone, friedelin, taraxasterol[15], and many other constituents[14,15].

S.costus has antiseptic[16], antibacterial [17,18](costicacid,dehydrocotuslactone,myrcene,pcymene, tannin[15]), antifungal[19,20] (caryophylleneoxide, myrcene, octanoicacid,pcymene[15]), antiviral[3,17,21-25](p-cymene,stigmasterol, tannin[15]), antiflu (lupeol, p-cymene[15]), anti-Epstein-barr virus(lupeol, betulin[15]), antinematodal[23,26], anthelmintic[23,27,28] (tannin[15]), anti-trypan0-osoma[6],anti-malarial[23,27] (lupeol[15]), anti-leishmanic (caryophyllene[15]), antiinflammatory[23,29-35], antioxidant[36,37] (myrcene, palmitic acid, stigmasterol, tannin[15]), anti-lipid peroxidation[37], antileukotriene-D4 (oleic acid[15]), immunostimulant[37,38] (inulin[15]), immunomodulating[23,39-41], analgesic[27,28,35] (myrcene, p-cymene[15]), antipyretic(beta-sitosterol[15]), bronchodilating[16] (caryophyllene[15]), expectorant (camphene, inulin, alpha-phellandrene, caryophyllene, hexanoic acid[15]), gastic cytoprotective[42-45] (caryophyllene[15]), antiulcer (tannin[15]), choleretic (oleic acid[15]), cholagogic[46], carminative[16,28],antispasmodic[23,47] (myrcene,saussurine[15]), antidiarrheal[23,48](tannin[15]),antibacillary (p-cymene, acetic acid, alpha-phellandrene, beta-ionone, beta-sitosterol, caryophyllene[15]) astringent[16], hepatoprotective[1,3,23,24,28] (tannin, p-cymene[15]), antihepatotoxic[49] (tannin[15]), hypoglycaemic[23] (inulin[15]), anti-hyperglycemic(lupeol[15]), hypolipidemic[50](beta-sitosterol[15]), hypocholesterolemic(inulin, oleic acid, stigmasterol, beta-sitosterol[15]), angiotensin converting enzyme (ACE) inhibitor (myrcene[15]), diuretic (friedelin[15]), antiedemic(caryophylline oxide, lupeol, taraxasterol[15]), antirheumatic (lupeol[15]), antidermatitis (caryophyllene[15]), anticancer[3,13,24,27,39,47,51-55] (caryophyllene oxide, caryophyllene, costunolide, lupeol, tannin, betulin[15]), sedating[16], and anticonvulsant properties[3,23,27,28,56] (myrcene[15]).

S. costus is used to treat, fever, headache, pain, cough, bronchial asthma[16,28,57-59], bacterial infections[17], diarrhea[23], cholera[57,59], typhoid[23,24], tuberculosis, leprosy[23,24,27], vomiting, dyspepsia[23,28], hiccups[27], gastric ulcer[3,23,43,44,60,61], abdominal pain[23,28], diarrhea[23], tenesmus[23], arthritis[3,24], rheumatoid arthritis, systemic lupus erythemaatosus, respiratory distress[41], chronic skin diseases[57,59], itching[28], scabies, ringworm, bruises, cuts[28,62,63], and diabetes mellitus[50].

COVID-19

COVID-19 has emerged as a pandemic and a public health crisis. The causative agent was named SARS-CoV-2 and was detected from throat swab samples[64]. It enters the cells by endocytosis after attachment to the angiotensin-converting enzyme-2 (ACE2) receptors on cells in the lung, gastrointestinal tract, blood vessels, heart, and kidney[65]. Many countries try to find a cure or vaccine to this disease. Clinical features of COVID-19 include tiredness, fever, dry cough, shortness of breath, myalgia, aches, nasal congestion, sore throat, nausea, vomiting, and diarrhea[66-68]. About 2-10% of COVID-19 infected patients have diarrhea, and the RNA of the virus could be detected in stool and blood samples[69]. Some cases are asymptomatic or lacking the typical symptoms of fever, dry cough and, fatigue, and the diagnosis is based on detection of the viral RNA in throat

swab samples[70]. In the majority of cases, the course of infection remains mild[71,72], and the patients resolve spontaneously[66]. The patients can develop bacterial and fungal infections as the disease progresses. Therefore, antibiotic or antifungal treatment may be given as appropriate[73]. Individuals with multiple comorbid conditions are prone to severe infection[67].

Fever can be treated with antipyretic drugs such as paracetamol, and patients with non-productive cough can be given expectorants such as guaifenesin[74]. Empirical early antibiotics were given for possible bacterial pneumonia[75].

Liver injury with various degrees may occur in patients with COVID-19 and the infection may be caused directly by the virus[72,76]. The incidence of liver injury ranged from 14.8-53%, detected mainly by abnormal alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) levels and mild elevation of bilirubin levels[67]. Gamma-glutamyl transferase and alkaline phosphatase were elevated in 54% and 18% of cases[77]. The incidence of liver injury in severe COVID-19 patients was higher than that in mild cases[67,78] and signs of hepatic dysfunction may occur in critically ill patients[72]. One study reported that serum ALT and AST levels increased up to 7590 U/L and 1445 U/L, respectively, in a severe COVID-19 patient. Also, reduced albumin levels may be detected in severe cases[66]. Postmortem biopsies showed moderate microvascular steatosis and mild lobular and portal activity, indicating that the injury may be due to either SARS-CoV-2 infection or drug-induced liver injury[79], which might be caused by lopinavir/ritonavir, that were used as antiviral therapy[80].

In COVID-19, various fatal complications including severe pneumonia, ARDS, pulmonary edema, septic shock, and organ failure can occur[66].

In some patients with SARS-CoV-2, there is overexpression of inflammatory mediators which is known as cytokine storm syndrome (CSS) which also occurs in other inflammatory conditions such as sepsis. It is unknown who will develop the cytokine storm. CRP, serum ferritin, and IL-6 are early biomarkers that may predict the evolution of CSS. These patients have a much higher incidence of a rapid deterioration of health and death[81]. The cytokine storm is triggered by an imbalanced response of type 1 and type 2 T helper cells[67,82].

Covid-19 patients had a thrombosis in the small vessels of multiple organs. SARS-CoV-2 facilitates endotheliitis that may precipitate thrombosis[83]. Respiratory failure in COVID-19 is not caused by ARDS alone[84], but microvascular thrombosis may play a role as well. This has important diagnostic and therapeutic implications[85]. Whether the thrombotic process is directly caused by the virus or by the local or systemic inflammation is not completely understood[86].

Hypertensive, diabetic, older patients and those with coronary heart disease were at higher risk of mortality[71,72]. Patients with myocardial injury are older and have a higher prevalence of coronary artery disease, hypertension, heart failure, and diabetes mellitus than those with normal levels of troponin I (TnI) or troponin T (TnT). Also, they have evidence of more severe systemic inflammation[87,88]. Patients with risk factors for atherosclerotic cardiovascular disease have a higher risk of developing acute coronary syndrome during acute infections which have been shown previously in clinical and epidemiologic studies of influenza[89-91], and other acute inflammatory conditions[92]. Such acute coronary events

could result from the severe increase in myocardial demand triggered by infections that precipitate myocardial injury or infarction, or respiratory dysfunction and hypoxemia caused by COVID-19. Alternatively, cytokines released during severe inflammation could lead to atherosclerotic plaque instability and rupture[93].

The mortality among all infected patients is about 0.5-4%[94], among patients who require hospitalization is about 5-15%, and for those who become critically ill is about 22-62%[72,74].

At present, there is no effective antiviral treatment or vaccine for COVID-19. Several drugs were tried[95]. Early initiation of antiviral treatment is known to decrease the severity of the disease[96]. Oseltamivir, a neuraminidase inhibitor, is currently being tried. Remdesivir acts as an adenosine-analog that induces RNA chain termination, it inhibited SARS-CoV-2 in vitro[97,98] and decreased the severity of MERS-CoV-infection in a non-human primate model in vivo[99]. Several reports have suggested it's clinical efficacy in patients with COVID-19[100,101]. Ritonavir-boosted lopinavir has an antiviral effect on SARS-CoV2 in vitro but not in vivo study[102]. Hydroxychloroquine or chloroquine phosphate has antiviral efficacy against SARS-CoV-2 in vitro by interference with the ACE2-receptor-mediated endocytosis and is used as monotherapy or in combination with azithromycin[98,103,104]. It is not recommended to use systematic corticosteroids for respiratory failure without ARDS in COVID-19, however, it may be used for patients with ARDS[105]. Glucocorticoids may be considered for patients with severe immune reactions[73,74]. Treatment with methyl prednisolone, 1-2 mg/kg/d for 5-7 days, is associated with a reduction in duration of fever and the need for supplemental oxygen[105]. The use of convalescent plasma may contribute to recovery[106]. Anti-cytokine therapy, as anti-IL-1 and anti-IL-6 may mitigate the hyper-inflammation that may develop in conjunction with ARDS[102,107].

Recent recommendations suggest that all hospitalized COVID-19 patients should receive thromboprophylaxis, or full therapeutic-intensity anticoagulation if needed[108]. In the absence of shock, intravenous fluids should be carefully administered when needed[109]. Patients with a severe respiratory infection, respiratory distress, hypoxemia, or shock require immediate oxygen therapy[110]. About 5-10 % of patients require intensive care unit admission and mechanical ventilation[94].

Possible rule of *S. costus* in treatment of COVID-19

S. costus by its myrcene content that acts on ACE receptors[15] may interfere with viral entry into the cells. *S. costus* is used to treat fever, headache, cough, and bronchial asthma[16,28,57-59]. Oleic acid acts as antileukotriene-D4[15] therefore acts as a bronchodilator. *S. costus* is traditionally used as a bronchodilator[16] and as an analgesic[27,28,35]. Myrcene and p-cymene have analgesic properties while camphene, inulin, alpha-phellandrene, caryophyllene, hexanoic acid act as expectorant[15.] *S. costus* has antimicrobial[17,18,23] and antibacterial properties[17,18] (costic acid, dehydrocotus lactone, myrcene, p-cymene, tannin[15]). It is traditionally used as antiseptic[16] and has a wide spectrum antimicrobial activity against some human pathogens. It exhibited a significant level of antibacterial activity against many Gram-positive and Gram-negative pathogenic bacteria, including staphylococcus aureus, pseudomonas aeruginosa, acinetobacter baumanii, escherichia coli, and klebsiella pneumonia[17].

Also, it has antifungal activity[19,20] (caryophyllene oxide, myrcene, octanoic acid, p-cymene[15]). The decoction of the plant increases the endogenous motilin release and accelerates gastric emptying[42], and improves gastric cytoprotection[43,44]. It amplified the mucus discharge and was proved to be an antiulcer agent[3,23,43,44,60,61]. Caryophyllene[15] and increased intracellular glutathione are responsible for protection against gastric cell injury[36]. Besides, *S. costus* showed the ability to inhibit several strains of helicobacter pylori[111] and it is carminative[16,28]. Oleic acid has choleretic effect[15] and costunolide has cholagogic effect[46]. *S. costus* has significant antidiarrheal activity[23,48] (tannin[15]), antiseptic and astringent agent[16]. It is widely utilized in different medical systems all around the world for treating a variety of ailments such as vomiting, dyspepsia, inflammation, diarrhea, tenesmus, and abdominal pain[23,28]. *S. costus* roots have hepatoprotective[1,3,23,24,28] (tannin, p-cymene[15]) and antihepatotoxic effects[49] (tannin[15]).

S. costus roots have antiviral activity[3,17,21-25]. The studies that demonstrated its antiviral activity were done on the hepatitis B virus (HBV) and showed its considerable activity against the virus and its ability to inhibit hepatitis B surface antigen (HBsAg) expression[22,25]. Constunolide and dehydrocostus lactone showed an inhibitory 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[22]. P-cymene, stigmasterol, tannin, lupeol, and botulin have antiviral effects[15]. *S. costus* has anti-inflammatory activity[23,29-35]. It is frequently used for inflammatory diseases. It inhibited the cytokine-induced neutrophil chemotactic factor induction[30]. Costunolide has antiinflammatory activity[33]. *S. costus* decreases pain and inflammation by inhibition of cyclooxygenase (COX) enzyme[35]. *S. costus* is used for treatment of chronic inflammation of the lungs, chest congestion, lung inflammation[29], and respiratory distresss[41]. Chlorogenic acid in the roots of *S. costus* exhibited antioxidant activity[36]. Myrcene, palmitic acid, stigmasterol, and tannin have antioxidant properties[15]. *S. costus* extract caused a dose-dependent protection against lipid peroxidation[37]. *S. costus* possesses immunostimulant effect[37,38] (tannin[15]). It increased the leukocytic count, phagocytosis and antibody-secreating cells[40]. It inhibited the oxidation of reduced glutathione (GSH) in a dose-dependent manner[37]. The importance of thiols, especially of cysteine and glutathione, for lymph-ocyte function, has been known for many years. GSH is a non-enzymic mode of defense against free radicals[112]. Glutathione is an important constituent of intracellular protective mechanisms against several noxious stimuli, including oxidative stress[113]. *S. costus* roots have immunomodulator activity[23,39-41]. Cynaropicrin has immunomodulatory effects on cytokine release[39]. *S. costus* has " complement-inhibitor'' substances helpful in the treatment of some diseases related to marked activation of the complement system, like rheumatoid arthritis, respiratory distress, and systemic lupus erythematosus[41]. Its roots are used in the treatment of rheumatic diseases[3,24,41]. Lupeol has antirheumatic effect[15]. *S. costus* has hypoglycaemic activity[23] (inulin[15]), and it was found to be effective for obese diabetic patients[50]. It showed a significant hypolipidaemic effect in rabbits. Reduction in serum triglycerides and cholesterol

were also found to be significant[50]. Beta-sitosterol has hypolipidemic and hypocholesterolemic effects, inulin, oleic acid, and stigmasterol have hypocholesterolemic effects[15]. *S. costus* roots have spasmolytic activeity[23]. Myrcene and saussurine have antispasmodic actions[15]. *S. cotus* is known to suppress contractions in the guniea-pig aorta. Sesquiterpenes are recognized to stimulate the soluble guanylyl cyclase (sGC) which stimulates extrusion of K+ ions and thereby reduces intrinsic Ca++ ions through activation of protein kinase G (PKG) pathway and cyclic guanosine monophosphate (cGMP), leading to smooth muscles relaxation[47].

Conclusion and recommendation:

Medicinal plants provide us with important drugs that could be used to treat different diseases. Research institutes should evaluate the therapeutic potential of *S. costus* in the treatment of COVID-19 and the patients should be asked to participate in clinical trials. It is worthy to separate the bioactive compounds from the roots of *S. costus* to get new natural and effective drugs.

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