International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 14, Special Issue 5, 2022

Review Article

QUST AL HINDI (*SAUSSUREA LAPPA)*: A NARRATIVE REVIEW OF ITS PHYTOCHEMISTRY AND PHARMACOLOGICAL POTENTIAL AGAINST COVID-19

SUKMAWATI S.[1,2], IDA MUSFIROH[1], MUCHTARIDI[1], ADRYAN FRISTIOHADY[3]

[1]Departement of Pharmaceutical Analysis and Medicinal Chemistry, Faculty of Pharmacy, Universitas Padjadjaran, Sumedang, Indonesia, [2]Departement of Chemical Pharmacy, Faculty of Pharmacy, Universitas Muslim Indonesia, [3]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Halu Oleo, Kendari Indonesia
***Email: ida.musfiroh@unpad.ac.id**

Received: 19 Sep 2022, Revised and Accepted: 09 Nov 2022

ABSTRACT

In 2020, the World Health Organization officially designated Coronavirus Disease 2019 (COVID-19) to be global pandemic. Response of immune to SARS-CoV-2 infection includes a hyper-inflammatory state. *Saussurea lappa* is a medical plant known in several traditional medical systems, such as Persian and Indian medicine. *S. lappa* has anticancer, antiviral, antirheumatic, anti-inflammatory, and hepatoprotective properties as clinically demonstrated. The purpose of this article to analyze the content of chemical compounds and possible pharmacological activities to fight COVID-19. As primary data sources for this study, researchers looked at articles about the possibility of *Saussurea lappa* as an alternative in the treatment of COVID-19. Data were gathered online through various academic papers published from 2012 to 2022 derived from the PubMed and Google Scholar databases.

One of the components of *Saussurea lappa* is myrcene which might act on ACE receptors. SARS-CoV-2 enters cells via endocytosis after binding to the ACE2 receptor. The anti-inflammatory properties of *Saussurea lappa* can be used to treat COVID-19 by reducing inflammatory cytokinins (TNF-α, IL-1β). Further study and clinical trials are needed to prove the effectiveness of *Saussurea lappa* against COVID-19 patients. *Saussurea lappa* has a important role in treating COVID-19 based on the effects of active phytochemical compounds that have anti-inflammatory activity, antioxidant, immunomodulator, antcancer, antihepatotoxic, and antihipertension. The *Qust al Hindi* has not yet been a final drug for the treatment of COVID-19 for it must go through clinical trials on COVID-19 patients directly.

Keywords: *Sausserea lappa*, *Saussurea costus,* Qust al hindi, COVID-19

DOI: https://dx.doi.org/10.22159/ijap.2022.v14s5.17 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

In 2020, *World Health Organization* (WHO) officially declared Coronavirus Disease 2019 (COVID-19) as a global pandemic. The first case found in Indonesia was 2 people confirmed by COVID-19, dated March 2nd, 2020 [1]. Coronavirus Disease 2019 (COVID-19) is an illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This has led to the current pandemic and is a global health emergency [2]. Immune response to SARS-CoV-2 comprises hyperinflammation, similar to the observed lymphohistiocytosis hemophagocytic where the increasing concentration of active C protein, ferritin, and interleukin-6 occurs [3].

Recently, none of the breakthroughs for antivirus vaccine and therapeutic drugs exists for COVID-19 treatment. Along with a defense strategy, continuous treatment is mainly focused on symptomatic and respiration support in line with diagnosis. Severe pneumonia atypical is the main cause of death in infected patients. Typically, the infected patients have mild infection symptoms of upper respiratory, having similarity to common flu attacks. Prognosis referring to the most common symptom of COVID-19 comprises fever (88-98%), congested upper respiratory, dried cough, fatigue, sore throat, asphyxiate, diarrhea, myalgia, and digestion disorders [4].

Coronavirus is a big family virus that can cause disease in animals or humans. The latest coronavirus identified to cause coronavirus disease is COVID-19. COVID-19 is an infectious disease caused by a recently discovered coronavirus. The viruses and disease were not known until the 2019 plague outbreak in Wuhan, China [5, 6].

COVID-19 triggers a response to immune inflammation. Release cytokines inflammation in COVID-19 cases causes storm cytokines and dysregulation of the immune system, producing syndrome disturbance respiration I and failure multiorgan [7]. Dietary supplements and herbs modulate function immunity and control adaptive and default immunity in a multidirectional manner [8]. The antivirus properties of dietary supplements and herbs have been attributed to various strains of viruses such as human immunodeficiency virus, hepatitis B and C viruses, herpes simplex virus, influenza virus, and earlier coronaviruses such as SARS and MERS [9].

There were many causes of COVID-19. Some causing factors were virus infection and immunity levels, such as increasing inflammation, cytokine content, and antibody production. Immune response to Sars-Cov2 infection was a hyperinflammation condition [10]. According to a study previously, herbal medicine was considered as the wrong one approach alternative for COVID-19 treatment. In China, the Commission Health National has state combined herbal medicine with Western medicine as a treatment for COVID-19 and has Secrete many guidelines about therapy related to herbal medicine [11]. Moment this; some clinical proof reports affect positive herb for COVID-19 treatment [12, 13]. Some people don't generally use herbal plants as treatment; however, at the moment many people are using herbs as herb or herbal concoction together with Covid-19 virus emergency [14]. Along with walking time, society could easily find herb without a recipe proven doctor effective against SARS CoV-2 [15].

Characteristically, *Saussure lappa* (syn *Saussurea costus*) is a straight and firm-stem herb with a height of 1-2 m. The roots are sturdy by 60 cm in size and have a typical and strong fragrance. A crossing slice shows the periderm, where phloem and xylem are seen. Its stem is firm and fibrous; the leaf has stalked and is 1 m in length. Its flower is dark bluish-purple to black. The flower head does not have a stalk, hard and rounded shape with a diameter of 3-5 cm. The length of the fruit is around 3 mm, curved, cupped, and condensed [16]. *Saussurea lappa (costus)* or more known by *qust hindi* is a medical plant popularly known in some traditional medication systems, such as Persia and India [17]. *Saussurea lappa* is the costus plant of the Compositae family. This plant is spotted in the Himalayas region, and its roots are largely used for various diseases due to its wider efficacy. Saussurea lappa is a native plant to India, Pakistan and China, where it grows in the Himalaya region at 2500-3500 m altitude [18]. Costus may play an important role in

treatment of COVID-19 as it can be used to treat fever, nausea, cough, and bronchial asthma. Besides that, sour oleate in costus Act as bronchodilator, and camphene, inulin, alpha-phellandrene, caryophyllene, and sour hexanoate as function expectorant. Besides that, costus have a number of substance blocker complement and effect immunomodulator on release cytokines, both of which could help in treating marked disease with existence marker inflammation [2, 19]. Use costus during pandemic in the community increased significantly. That being said, the number of patients treated for COVID-19 at home was significantly lower among user compared with non-users (22% vs. 34%; p = 0.0095), although not on significant level if other variable regulation [20]. *Qusthul hindi* is not a definitive drug for the treatment of Covid-19 patients, but it is a recommendation for additional supplements or prevention and early treatment for Covid-19 patients [21].

Costus (*S. lappa*) is known mostly in prophetic medicine as well as in Ayurveda, Unani, and Siddha. This plant contains phytochemicals from various classes of chemicals, such as alkaloids, glycosides, coumarins, flavonoids, phenols, quinones, steroids, tannins, and terpenoids. Costus has many pharmacological effects, including anticancer, antiinflammatory [22], immunomodulatory, CNS depressants, and antimicrobial [23, 24], anti-fungal [25], anti-diabetic [26], antihelmintic [27], anti-tumor [25], anti-ulcer [28], immunostimulant [29], and anti-hepatotoxic [30]. It is traditionally used to treat pneumonia, coughs, colds, ulcers, and also rheumatism [31].

Based on previous research (table 1) it had been explained some pharmacology effects of this plant, such as anti-inflammation, anti-virus, anti-oxidant, immunomodulator, immunostimulant, hepatoprotective, antihipertension, etc.

Table 1: Research related to the *Saussurea lappa* in the treatment of covid-19

No.	References	Pharmacology target	Research
1	[4]	Antiviral activities	*Saussurea lappa* is used for anti-virus. The phytochemical substances isolated from this plant are *costunolide, isodihydrocostunolide, chloropicrin,* etc.
2	[10, 63]	Anti-anxiolytic and antidepressant	There are many causes of Covid-19, such as virus infection, immune system level, declining inflammation, cytokine concentration, and antibody production. The immune response to Covid-19 infection is hyperinflammation.
3	[16, 20]	Anti-inflammation, anti-ulcer, anti-cancer, and hepatoprotective	The ability of *Saussurea costus* in its activity is anti-inflammation, anti-ulcer, anti-cancer, and hepatoprotective
4	[19]	Immunomodulator effect	*Saussurea costus* plant can be the treatment for Covid-19 and cure. There are many bioactive phytochemical molecules, having some characteristics, such as antiseptic, anti-bacterial, anti-fungal, anti-virus, ant-inflammation, anti-oxidant, anti-lipid peroxidase, immunostimulant, immunomodulation, analgesic, a bronchodilator, hepatoprotective, and anti-hepatotoxic.
5	[20]	Bronchodilator, expectorant	Covid-19 triggers inflammation response. The use of herbal medicines to fight against Sars-Cov2 aims for anti-virus, anti-inflammation, anti-oxidant, and preventive measures. *Costus* has some inhibiting complement substances and immunomodulator effects in cytokine releasing that can aid in curing diseases marked by inflammation.
6	[21]	Respiratory system disorder, throat issue, lungs inflammation, and fever	*Qusthul hindi* is not a final drug for Covid-19 infection, but it is a recommendation for additional supplements or prevention and early treatment for Covid-19 patients.
7	[32]	Anti-inflammation, anti-Alzheimer, anti-diabetic	Ethnopharmacology of roots and leaves from *Saussurea lappa* is used in traditional medication, such as throat infections, cough, and asthma. *Saussurea lappa* is reported as anti-microbe, larvicide, anti-oxidant, anti-hepatotoxic, anti-inflammation, anti-cancer, anti-ulcerous, anti-convulsant, anti-diabetic, and anti-Alzheimer.
8	[34]	Anti-inflammation,	Sesquiterpene effect isolated from *Saussurea lappa* in inhibiting TNF-α secretion, in which the main component is *costunolide*, showing activity of TNF-α inhibiting.
9	[37]	Anti-inflammatory, immunomodulator, antidote, antiseptic, disinfectant expectorant	*Unani* drug to Covid-19 has antioxidant, anti-virus, immunomodulator, anti-parasite effect, antiseptic, antidote, and expectorant. *Saussurea lappa* acts in pharmacologic activities, such as hepatoprotective, anti-inflammation, immunomodulator, antidote, antiseptic, disinfectant, and expectorant.
10	[38]	Cellular immune response, such as Th2, Th17, and NK cells, and humoral immune response, such as TGF-β, IL-17A, sigA, IL-4, IL-4, B-def, and IgG.	The component of *Saussurea* costus, which is myrcene, can work in the ACE receptor. Sars-Cov2 enters cells via endocytosis after attaching to the ACE2 receptor. If myrcene functions as an epitope, it will result in an antibody attaching to the ACE2. Then, Sars Cov2 cannot enter cells via endocytosis after attributing.
11	[39]	Oxidative stress, inflammation, and apoptosis	*Saussurea lappa* has a tremendous protective effect via its activity of anti-inflammation, anti-apoptosis, and anti-oxidant, so it can be a better candidate as a natural anti-oxidant to deal with the side effects of dangerous glucocorticoids.
12	[44]	Hepatoprotective, hypoglycemic, antidiabetic, anti-inflammatory, antiviral, and antifungal effects	*Saussurea lappa* plant contains active substances, such as *saussurine, and costunolide lactone*, and the pharmacology activity of this plant reportedly has hepatoprotective effects, hypoglycemic, anti-diabetic, anti-inflammation, anti-virus, and anti-fungal.
13	[51]	Anticancer, antiulcer, hepatoprotective, anti-viral, anticonvulsant, antiarthritic, Activities	*Saussurea lappa* has some activities of anti-cancer, anti-ulcer, hepatoprotective anti-virus, anti-convulsant, and anti-rheumatic. The actively biological substances are lactone cynaropicrin, dehydrocostus, germacrene, and lappadilactone.
14	[51]	Anti-cancer, inflammation, ulcer, virus infection, and microbe	*Costunolide* is an active lactone sesquiterpene isolated from the *Saussurea lappa* plant pharmacologically. It has characteristics as a treatment for cancer, inflammation, ulcer, skin, virus and microbe infection, etc.
15	[51, 52]	Anticancer, anti-inflammatory, anti-hepatotoxic, anti-viral,	The phytochemical of *Saussurea lappa* is *sesquiterpenes, flavonoid, lignan, phytosterol alkaloid, terpenes, and anthraquinones*. The pharmacology of *Saussurea lappa* is anti-cancer, anti-inflammation, gastroprotective and gastric, anti-hepatotoxic, anti-ulcer and *colagegic*, anti-virus, anti-microbe, and anticonvulsant.
16	[72]	Cough and asphyxiate	Patients contaminated by Covid-19 were negative and the patient stated during the interview that *"qutshul hindi* is wood from the southern Arabia and India. After drinking it *(Qutshul Hindi)*, cough and asphyxiate are lessen, and I can talk fluently up now*"*
17	[73]	Anti-arthritic, immune and antioxidant response	Extract of *Saussurea lappa* has an anti-rheumatic activity that is beneficial and improves immune response and anti-oxidant from monoarthritis, induced by adjuvant in mice.

Anti-inflammation

The anti-inflammatory nature of a drug could be used to cure COVID-19. Also, the decline of inflammation cytokinin (TNF-α, IL-1β) would be effective in treatment. Costunolide had an inhibiting effect in the expression of IL-1β gen, and a different lactone had an anti-inflammation effect [16]. Particularly, *Saussurea lappa* had those substances, so that it could be COVID-19 medication, and further research of the clinical test was expectedly to be conducted to prove the efficacy of *S. lappa* in COVID-19 patients. Covid-19 triggers inflammation response. The use of herbal medicines to fight against Sars-Cov2 aims for anti-virus, anti-inflammation, anti-oxidant, and preventive measures. *Costus* has some inhibiting complement substances effects in cytokine releasing that can aid in curing diseases marked by inflammation [20]. There are many causes of Covid-19, such as virus infection, immune system level, declining inflammation, cytokine concentration, and antibody production. The immune response to Covid-19 infection is hyperinflammation [10, 63]. Ethnopharmacology of roots and leaves from *Saussurea lappa* is used in traditional medication, such as throat infections, cough, and asthma. *Saussurea lappa* is reported as anti-inflammation [32]. Some active substances of *Saussurea lappa*, such as ethanol, costunolide, dehydrocostus lactone, etc., had an anti-inflammatory role, which also took a role in the growth of the SARS-CoV-2 virus.

Saussurea lappa under a dosage of 50-200 mg/kg was found for acute and chronic inflammation as induced in mice. This extract described a sufficiently large value for the activity of anti-inflammation via feet endemic induced by carrageenan and peritonitis animal model showing antiinflammation effect [33]. An active compound of costunolide was known for its antiinflammation effect. Costunolide compound inhibit interleukin 1b (1L-1b) protein and mRNA expression LPS-stimulated RAW 264.7 cells. Additionally, it suppressed transcription activity of AP-1 confirmed by electrophoresis mobility shifting test (EMSA) and inhibited mitogen-activated protein kinase phosphorylase (MAPK), which comprised of specific inhibitors, such as SAPK/JNK and p38 MAP kinase. Based on these activities, the mechanism of anti-inflammation activity from costunolide was proven [21]. *Saussurea lappa* had some complementary inhibitor substance and immunomodulatory effect in cytokine releasing, where both could aid in curing disease shown by inflammation marker [19]. Dehydrocostus lactone for osteoblast oxidative damage was observed and it showed a sufficiently large increase in the growth of osteoblast and hydrogen peroxide. In the dosage of 0.4-2 g/ml, calcium deposition, collagen, and alkaline phosphatase increased. The results showed that dehydrocostus lactone has the potency to fight osteoblast oxidative damage [20]. Sesquiterpene effect isolated from *Saussurea lappa* in inhibiting TNF-α secretion, in which the main component is *costunolide*, showing activity of TNF-α inhibiting [34].

Anti-virus/microbe

Saussurea lappa is used for anti-virus. The phytochemical substances isolated from this plant are *costunolide, isodihydrocostunolide, chloropicrin,* etc. In addition, *Saussurea lappa* has antimicrobial activity against Gram-positive and Gram-negative bacteria [4, 35]. Using North Blotting and human *in vivo* detection dose-dependent (IC50 value were 1.0 and 2.0 mmol assays, two substances of *costunolide* and *dehydrocostus* lactone, inhibited Hepatitis B surface antigen (HBsAg) was expressed in the liver cancer a HepA2 cell line derived from HepG2 cells. Bsed on observation, it was demonstrated that the tested substances showed significant HBV acitivity [36, 67].

The ethanol extract was known for anti-microbe activity by using *S. mutan*. The results displayed that the extract (higher than a dosage of 0.5–4 mg/ml) has a significant result ($p<0.05$) in suspending growth, acid production, and insoluble glucan formation. Also, it decreases the compliance of *S. mutan* in the synthesis test of soluble glucan for 2-4 mg/ml significantly [37].

In addition, ethanol extract of *Saussurea lappa* was also determined to *in vitro* study of anti-bacterial using five different strains derived from *Helicobacter pylori*. Under 40 g/ml dosage, it showed a higher third minimal inhibitory concentration as tested with other plant samples. The research also revealed that the antibacterial effect of plants is caused by the existing atsiri oil [38].

Anti-oxidant

Saussurea lappa has a tremendous protective effect via its activity of anti-oxidant, so it can be a better candidate as a natural anti-oxidant to deal with the side effects of dangerous glucocorticoids [39]. Flavonoid and *unani* drug to Covid-19 has antioxidant [37]. The content of total phenolic and flavonoid from n-butanol fraction of S. lappa was 44.43 µg gallic acid equivalent to (GAE)/g extract and 92.15 µg quercetin equivalent to (QE)/g extract which were determined by the Folin-Ciocalteu colorimetric method and aluminum nitrate, respectively, were higher than other solvent fractionation. The n-butanol fraction of S. lappa (1.000 ppm) showed the strongest inhibition potential on the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical and the reducing power was 92.98% and 0.38, respectively. Thus, it shows that S. lappa plants may help prevent antioxidant stress [40].

The antioxidant activity test of the extract was calculated as the percentage of peroxidation inhibition in the linoleic acid system [41]. The percentage inhibition of linoleic acid oxidation by water extracts of *Saussurea lappa*, were found to be moderate, ranging from 53-72.4%. This is related to the high content of phenolic compounds in this extract [42, 71]. Costus water extract has phenolic compounds (80 mg gG1 dry weight) than cidir (62 mg gG1 dry weight), and has significant and anti-scavenging effect [43].

Saussurea lappa is also known to contain phytochemical compounds such as costunolide, dehydrocostus lactone, caustic, palmitic, linoleic acid, sitosterol, cyclocostunolide, allantolactone, cyclocostunolide, isoalantolactone. The compounds have antidiabetic, antioxidant, anti-inflammatory and antimicrobial activity [44]. Water extract of costus is richer with compound phenolic which has an antioxidant and enhancement effect on bacteria probiotics cidir (*Ziziphus spina-christi* L.) real [34]. In addition, antioxidant activity can also prevent or treat COVID-19, oxidative mechanisms play a key role in the pathogenesis of almost all human diseases, and consequently antioxidants share a broad range of protective effects [45]. The mechanism of antioxidant activity is through ways to counteract the action of oxidants by scavenging reactive oxygen species (ROS) and by inhibiting enzymes that produce oxidants. Overproduction of ROS and deficiency of antioxidant systems play a major role in the incidence, progression and severity of COVID-19 [46, 66].

Oxidative stress is actively involved in the initiation and response mechanisms of viral respiratory infections to homeostatic system. Therefore, it is important to stop systemic inflammation to quench the cytokine storm caused by reactive oxygen species production. Antioxidants such as vitamin C, melatonin, quercetin, glutathione, astaxanthin, polyphenols, fat-soluble vitamins, and polyunsaturated fatty acids have been used in experimental and clinical studies for influenza, pneumonia, and other respiratory disorders get confirmed. The use of antioxidant is justifiable and will likely increase their effectiveness against the new coronavirus [47]. *Saussurea lappa* plants have several compounds that have pharmacological effects including anti-oxidant effects. It is expected that consuming *Saussurea lappa* plants can increase antioxidants in the body so that they can prevent or deal with the spread of COVID-19.

Anti-hepatotoxic

Saussurea lappa plant contains active substances, such as *saussurine, and costunolide lactone*, and the pharmacology activity of this plant has reportedly hepatoprotective effects, anti-inflammation, anti-virus [44]. Soggy extract and roots methanol of *Saussurea lappa* were tested for a hepatotoxic activity to D-galactosamine (D-GalN) and hepatitis, induced by lipopolysaccharide (LPS) in mice. Further, the pre-treatment of mice with different SL dosages caused an increase in creatinine plasma content by a means of depending on dosage and the extent of AST and ALT. Meanwhile, the post-treatment resulted in limited growth of liver breakdown, induced by DgalN and LPS. The study showed that root extract works better in fighting against hepatotoxic activity [34].

Constunolide and *dehydrocostus* lactone (isolated from *Sausserea lappa*) had fewer effects on the cell's life cycle. However, they depicted a delaying effect on human hepatoma Hep3B cells and the

expression of antigen on the surface of hepatitis B (HbA1g). The substance was proven to interrupt HbsAg by Hep3b cell. The research showed that *costunolide* and *dehydrocostus* lactone have potential to be develop as anti-HBV drugs in the future.

Immunomodulator

Saussurea costus plant can be the treatment for Covid-19 and cure. There are many bioactive phytochemical molecules, having some characteristics, such as immunostimulant and immunomodulation [19]. Extract plant *S. lappa* not only as anti-inflammatory and antioxidant but have a number of compound other like costunolide and dehydrocostus lactone which is as immumodulators, which act as blocker activity murder cytotoxic T lymphocytes. Use immunomodulators for increase immunity or power. Found that SARS-CoV-2 sufferers experience drop amount T or lymphocytes lymphopenia [48].

Compound costunolide and dehydrocostus lactone *Sausserea lappa* Act as blocker activity murder from cytotoxic T lymphocytes (CTL), via prevention enhancement phosphorylation tyrosine, costunolide hinder activity CTL assassination as response to binding cross receptors T cells as blocker function CTL assassination and induction molecule intracellular adhesion-1, dedydrocostus lactone from plant *Sausserea lappa* and guaianolide other checked for connection activity structure [49]. Confirmed that part guaianolide show effect sufficient inhibition big to induction molecule adhesion between cells-1 and kill function from CTL [50, 62].

Anti-cancer

The phytochemical of *Saussurea lappa* is *sesquiterpenes, flavonoid, lignan, phytosterol alkaloid, terpenes, and anthraquinones*. The pharmacology of *Saussurea lappa* is anti-cancer. Active components of *Saussurea lappa* are phenol and flavonoid. The use is for anti-cancer, hepatoprotective, anti-inflammation, and anticonvulsant [51]. Sesquiterpene lactone was tested to observe anticancer activity in a non-small cell lung cancer cell lines such as A549, NCI-H460, and NCI-H520. DHE-induced apoptosis and A549 and NCIH460 suspension cell lines and their activity hav been demonstrated by *in vitro* and *in vivo* methods [52]. The gastric cancer activity of the ethanolic extract was analyzed. Studies conducted on AGS gastric cancer cells and their treatment hypothesized that dose (80 g/ml) and time (48 h)-related apoptosis have been shown to cure gastric cancer in combination with conventional chemotherapy [32].

Hexane extract of *Sausserea lappa* was observed to chemo prevention measures in autonomous androgen prostate cancer and apoptosis induction in DU145 cells. This study showed that *dehydrocostus* lactone isolated with hexane extract of *Sausserea lappa* induces apoptosis in the cell line of human autonomous androgen prostate cancer in DU145 and inhibits cell growth [53].

Costunolide was sesquiterpene lactone isolated from *Sausserea lappa*. Also, it had a carcinogenesis effect by gen reporter test, and it was convinced by tumor-supporting phorbol ester 12-Otetradecanoylphorbol-13-acetate at the cell level. Then, the activity of synthase oxide nitrate was reinforced by tumor-promoting phorbol ester 12-O-tetradecanoylphorbol-13-acetate, consecutively repressed by *costunolide* with an IC_{50} value of 2 mmol/l [54].

Anti-hypertensive

The component of *Saussurea* costus, which is myrcene, can work in the ACE receptor. Sars-Cov2 enters cells via endocytosis after attaching to the ACE2 receptor. If myrcene functions as an epitope, it will result in an antibody attaching to the ACE2. Then, Sars Cov2 cannot enter cells via endocytosis after attributing. One of the components from *Saussurea lappa* was myrcene which could work in the angiotensin-converting enzyme 2 (ACE2) receptor. The angiotensin-converting enzyme 2 (ACE2) is an enzyme attaching to the outer cell surface (membrane) in some organs, such as the lungs, arteria, heart, kidneys, and duodenum. ACE2 worked to catalyze angiotensin II (a peptide vasoconstrictor) changes into angiotensin 1-7 (a vasodilator). ACE2 fights enzyme activity of the angiotensin-converting enzyme (ACE) by reducing the total of angiotensin-II and increasing angiotensin [38]. Sars-CoV2 entered the cell by endocytosis, after attaching to the ACE2 receptor. It was proven by the ease of the Covid-19 virus spreading globally and causing a pandemic than SARS-CoV. The existence of over-expression of ACE2 in humans would increase the severity of the infectious disease of Covid-19. If myrcene functioned as an epitope, it would produce an antibody attaching to ACE2, so Sars-CoV2 could not penetrate the cell through endocytosis after affixing [55, 19]. Besides myrcene substance, other substances contained by S. lappa were magnolialide that had, based on the comparison of a binding energy value, a lower value and stable interaction than other substances, so it had the best ability to obstruct the attaching of S-RBD with ACE2 and take a role as anti-virus SARS-CoV-2 [56, 65].

A number of studies previously has confirmed that compound-experienced bioactive agents could treat or deal with novel SARS-CoV-2 because they have significant anti-viral activity [57, 58]. Particularly, 28 vital substances were found in 25 articles (table 1), such as myrcene, oleate acid, champene, inulin, alpha-phellandrene, caryophyllene, hexanoate acid, costate acid, dehydrocotus lactone, p-cymene, tannin, costunolide, lupeol, chlorogenic acid, palmitate acid, atsiri oil, cynaropicrin, beta-sitosterol, saussure amines, sesquiterpenes lactone, pentylenetetrazol, hexane, ethanolic extract, methanolic extract, epiligulyl oxide and elecampane camphor, Acetone, aqueous, and lappa dilactone [59, 61].

Table 2: Phytochemical active compounds of *Saussurea lappa*

No.	Phytochemical active compound	Pharmacologic/Therapeutics	References
1	Myrcene	Inhibiting virus entering a cell, fever, headache, cough, bronchial asthma, analgesic, anti-microbe, anti-bacterial, anti-oxidant, antispasmodic, acting on the ACE receptor.	[19, 55, 71]
2	Oleate acid	Anti-leukotriene (bronchodilator), analgesic, choleretic effect, hypocholesterolemia	[20]
3	Champene	Expectorant	[19, 20]
4	Inulin	Expectorant, hypoglycemic activity, anti-diabetic, obesity, cholesterol, triglyceride, hypocholesterolemia	[19, 20, 70]
5	Alpha-phellandrene	Expectorant	[19, 20]
6	Caryophyllene	Expectorant	[19, 20, 50]
7	Hexanoate acid	Expectorant	[19, 20]
8	Costate acid	Antibacterial, antifungal	[19]
9	Dehydrocostus lactone	Antibacterial, antifungal, antivirus, anticancer, antiinflammation, angiogenesis effect, immunomodulator, anti-microbe, immunostimulant, anti-hepatotoxic, antidiabetic, hepatoprotective, gastric function, gastroprotective, hypotensive	[5, 16, 19, 36, 40-44, 34, 50, 69]
10	p-cymene	Anti-bacterial, antifungal, hepatoprotective, antivirus	[19]
11	Tannin	Anti-bacterial, antifungal, antidiarrhea, hepatoprotective, anti-hepatotoxic, anti-virus, antioxidant, immunostimulant	[19, 20]
12	Costunolide	Anti-virus, antiinflammation, colagogic effect, inflammation, angiogenesis effect, carcinogenesis effect, gastroprotective effect, immunomodulator, anti-microbe, immunostimulant, anti-hepatotoxic, anti-diabetic, anti-cancer, hepatoprotective, anti-tumor, anti-ulcer, hypotensive, anti-fungal, inflammation, ulcer, skin, virus and microbe infection	[16, 19, 34-36, 40-44, 49, 50, 54, 68]

No.	Phytochemical active compound	Pharmacologic/Therapeutics	References
13	Lupeol	Antivirus, anti-rheumatic	[19]
14	Chlorogenic acid	Anti-oxidant	[19]
15	Palmitate acid	Anti-oxidant	[19]
16	Atsiri oil	Anti-bacterial, anti-inflammation, anti-Alzheimer, anti-diabetic	[35, 40, 32]
17	Cynaropicrin	Immunomodulator, rheumatoid arthritis, respiratory disorder, lupus erythematosus systemic, anti-cancer, anti-inflammation	[19, 35, 40-42, 44]
18	Beta-sitosterol	The hypolipidemic effect, hypocholesterolemia	[19]
19	Saussureamines	Antispasmodic, gastric function, gastroprotective	[19, 41, 44]
20	Sesquiterpenes lactone	Stimulating soluble guanylyl cyclase (sGC), suppressing contraction in Guinea-pig's aorta, anti-inflammation, immunomodulator effect, anti-cancer, gastroprotective effect, anti-viral, spasmolytic activity	[19, 35, 41, 43]
21	Pentylenetetrazol	Anti-convulsant	[35]
22	Hexane	Anti-viral, anti-cancer, anti-inflammation, anti-fungal, anti-bacterial	[36, 41, 34, 49]
23	Ethanolic extract	Gastric carcinoma effect, anti-inflammation, antimicrobe, anticancer, anti-arthritis, immune and antioxidant responses	[35, 37, 41, 43, 44, 50]
24	Methanolic extract	Angiogenesis effect, anti-hepatotoxic, antiinflammation, antidiarrhea, gastroprotective effect, anticonvulsant, antiparasite, antibacterial, antifungal	35, 41-44, 49, 52]
25	Epiligulyl oxide and elecampane camphor	Antiallergy, antiasthma, anti-inflammation	[36]
26	Acetone	Collagenic effect and anti-ulcer	[41]
27	Aqueous	Anti-hepatotoxic, immunomodulator, hypolipidemic	[41-44]
28	Lappa dilactone	Anti-cancer	[42, 44]

CONCLUSION

Saussurea lappa has a potential role in the treatment of COVID-19 based on its phytochemical compounds effect to treat inflammation, as anticancer, antiviral and antimicrobial, antioxidant, antihipetension, immunomodulator, and antihepatotoxic. The Qust Alhindi has not become a final drug for COVID-19 medication since it must pass a clinical test for COVID-19 patients directly. However, it can be recommended as an additional supplement to prevent early treatment for COVID-19 patients or other suffering patients. To obtain a new and effective drug for COVID-19, research institutions must evaluate the therapeutic effectiveness of *Saussurea lappa* in medication and involve patients in the clinical test.

ACKNOWLEDGMENT

This research supported by Universitas Padjadjaran and Universitas Muslim Indonesia.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors have no conflict of interest.

REFERENCES

1. Al-Islam MS. Saussurea costus may help in the treatment of COVID-19. Sohag Med J. 2020;24(3):1-17.
2. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-13. doi: 10.1016/S0140-6736(20)30211-7, PMID 32007143.
3. Madhuri K, Elango K, Ponnusankar S. Saussurea lappa (Kuth root): review of its traditional uses, phytochemistry and pharmacology. Orient Pharm Exp Med. 2012;12(1):1-9. doi: 10.1007/s13596-011-0043-1.
4. Jubayer MF, Kayshar S, Mazumde AR, Akter SS. A review of five medicinal plants considering the therapeutic potentials in the management of COVID-19. Sylhet: Department of Food Engineering and Technology Sylhet Agricultural University-3100. Bangladesh; 2020.
5. World Health Organization. Q and A on coronaviruses (COVID-19). Available from: https://www.who.int/news-room/q-a-detail/q-a-coronaviruses. [Last accessed on 21 Mar 2020].
6. Islam MT, Sarkar C, El-Kersh DM, Jamaddar S, Uddin SJ, Shilpi JA. Natural products and their derivatives against coronavirus: a review of the non-clinical and pre-clinical data. Phytother Res. 2020;34(10):2471-92. doi: 10.1002/ptr.6700, PMID 32248575.
7. Azkur AK, Akdis M, Azkur D, Sokolowska M, van de Veen W, Bruggen MC. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. Allergy. 2020;75(7):1564-81. doi: 10.1111/all.14364, PMID 32396996.
8. Wang K, Conlon M, Ren W, Chen BB, Ba˛Czek, T. Natural products as targeted nodulators of the immune system. J Immunol Res. 2018:1-8.
9. Xian Y, Zhang J, Bian Z, Zhou H, Zhang Z, Lin Z. Bioactive natural compounds against human coronaviruses: a review and perspective. Acta Pharm Sin B. 2020;10(7):1163-74. doi: 10.1016/j.apsb.2020.06.002, PMID 32834947.
10. Prawiro SR, Anam K, Prabowo B, Bramanthi R, Fitrianingsih AA, Yuni D. Generating the responses immune with honey, saussurea costus, and nigella sativa in cellular and humoral may resolve COVID-19? Syst Rev Pharm. 2021;12(1):1588-93.
11. Ang L, Lee HW, Choi JY, Zhang J, Soo Lee M. Herbal medicine and pattern identification for treating COVID-19: a rapid review of guidelines. Integr Med Res. 2020;9(2):100407. doi: 10.1016/j.imr.2020.100407, PMID 32289016.
12. Chan KW, Wong VT, Tang SCW. COVID-19: an update on the epidemiological, clinical, preventive and therapeutic evidence and guidelines of integrative Chinese-western medicine for the management of 2019 novel coronavirus disease. Am J Chin Med. 2020;48(3):737-62. doi: 10.1142/S0192415X20500378, PMID 32164424.
13. Maria PMN, Santy IP, Zainur R, Wiliarisa PP, Astri Y, Artha BSD. Penggunaan herbal dalam menghadapi pandemi covid-19: a systematic reviewe. J Health Res. 2022;5(1):37-49.
14. Illian DN, Siregar ES, Sumaiyah S, Utomo AR, Nuryawan A, Basyuni M. Potential compounds from several Indonesian plants to prevent SARS-CoV-2 infection: a mini-review of SARS-CoV-2 therapeutic targets. Heliyon. 2021;7(1):e06001. doi: 10.1016/j.heliyon.2021.e06001, PMID 33532640.
15. Welz AN, Emberger-klein A, Menrad K. Why people use herbal medicine: insights from a focus-group study in Germany. BMC Complement Altern Med. 2018;18(1):92. doi: 10.1186/s12906-018-2160-6, PMID 29544493.
16. Sanna AK, Al-Elyani RA, Dalia MD. Histological and ultrastructural studies on the effect of costus plant and amphotericin B on male lung rats infected by Aspergillus niger. Life Sci J. 2012;9(4):5321-38.
17. Harshita KS, Gautam S, Joshi RK, Sahu AK. A pragmatic plan for the mental health consequences during Covid-19 pandemic through Ayurdeva. Int J Ayurdeva Pharm Res. 2021;9(9):86-90.

18. Rao RN, Raju SS, Babu KS, Vadaparthi PRR. HPLC determination of costunolide as a marker of Saussurea lappa and its herbal formulations. Int J Biochem. 2013;3(1):99-107.
19. Chang KM, Choi SI, Kim GH. Antioxidant activity of Saussurea lappa C.B. Clarke Roots. Preventive Nutrition and Food Sciences. 2012;17(4):306-9.
20. Ahmad S, Zahiruddin S, Parveen B, Basist P, Parveen A, Gaurav. Indian medicinal plants and formulations and their potential against COVID-19-preclinical and clinical research. Front Pharmacol. 2020;11:578970. doi: 10.3389/fphar.2020.578970. PMID 33737875.
21. Aldwihi LA, Khan SI, Alamri FF, Alruthia Y, Alqahtani F, Fantoukh OI. "Patients" behavior regarding dietary or herbal supplements before and during Covid-19 in Saudi Arabia. Int J Environ Res Public Health. 2021;18(10):1-14. doi: 10.3390/ijerph18105086, PMID 34064950.
22. Yashvanth S, Robinson A, Babu KS, Naidu VGM, Vishnuvardhan MVPS, Ramakrishna S. Anti-inflammatory and cytotoxic activity of chloroform extract of roots of Saussurea lappa Clarke. J Pharms Res. 2010;3(8):1775-8.
23. Julianti T, Hata Y, Zimmermann S, Kaiser M, Hamburger M, Adams M. Antitrypanosomal sesquiterpene lactones from Saussurea costus. Fitoterapia. 2011;82(7):955-9. doi: 10.1016/j.fitote.2011.05.010, PMID 21624443.
24. Khalid A, Uzair-ur-Rehman SA, Khilji S, Fatima U, Khan MI. Antimicrobial activity analysis of extracts of Acacia modesta, Artimisia absinthium, Nigella sativa and Saussurea lappa against gram positive and Gram negative microorganism. Afr J Biotechnol. 2011;10:4574-80.
25. Ko SG, Kim HP, Jin DH, Bae HS, Kim SH, Park CH. Saussurea lappa induces G2-growth arrest and apoptosis in AGS gastric cancer cells. Cancer Lett. 2005;220(1):11-9. doi: 10.1016/j.canlet.2004.06.026, PMID 15737683.
26. Upadhyay OP, Singh RH, Dutta SK. Studies on antidiabetic medicinal plants used in Indian folklore. Aryavaidyan. 1996;9:159-67.
27. Seki K, Hashimoto A, Kobayashi H, Kawahara Y, Yamahara J. Motility inhibitory effect on Anchusan and Jintan and its active components in Anisakis type larvae. Yakuri To Chiryo. 1991;19:265-89.
28. Sutar N, Garai R, Sharma US, Singh N, Roy SD. Antiulcerogenic activity of saussurea lappa root. Int J Pharm Life Sci. 2011;2:516-20.
29. Hamilton AC. Medicinal plants, conservation and livelihoods. Biodivers Conserv. 2004;13(8):1477-517. doi: 10.1023/B:BIOC.0000021333.23413.42.
30. Yaeesh S, Jamal Q, Shah AJ, Gilani AH. Antihepatotoxic activity of saussurea lappa extract on D-galactosamine and lipopolysaccharide-induced hepatitis in mice. Phytother Res. 2010;24Suppl 2:S229-32. doi: 10.1002/ptr.3089, PMID 20041433.
31. Pandey MM, Rastogi S, Rawat AKS. Saussurea costus: botanical, chemical and pharmacological review of an ayurvedic medicinal plant. J Ethnopharmacol. 2007;110(3):379-90. doi: 10.1016/j.jep.2006.12.033, PMID 17306480.
32. Shah NC. Kustha, Saussurea costus (Saussurea lappa): its unexplored history from the Athrvaveda. IJHS. 2019;54(4).
33. Sun J, He WT, Wang L, Lai A, Ji X, Zhai X. COVID-19: epidemiology, evolution, and cross-disciplinary perspectives. Trends Mol Med. 2020;26(5):483-95. doi: 10.1016/j.molmed.2020.02.008, PMID 32359479.
34. Duraipandiyan V, Al-Harbi NA, Ignacimuthu S, Muthukumar C. Antimicrobial activity of sesquiterpene lactones isolated from traditional medicinal plant, Costus speciosus (Koen ex.Retz.) Sm BMC Complement Altern Med. 2012;12(13):13. doi: 10.1186/1472-6882-12-13, PMID 22397713.
35. Jubayer MF, Kayshar S, Mazumde AR, Akter SS. A review of five medicinal plants considering the therapeutic potentials in the management of COVID-19. Sylhet: Department of Food Engineering and Technology Sylhet Agricultural University-3100. Bangladesh; 2020.
36. Ahmad W, Tauleha S, Zulkifle M, Sofi G. Role of unani medicine in prevention and treatment of waba (Epidemics) including COVID-19: a review. Eur J Cell Sci. 2020;2(1):1-9. doi: 10.34154/2020-EJCS-0201-01-09/euraass.
37. Farooqui S, Quamri M, Basheer R, Baig S, Ahmed K, Ahad M. COVID-19 Pandemic–perspective through unani medicine. J Res Tradit Med. 2020;6(2):37-46. doi: 10.5455/jrtm.2020/67262.
38. Amara U, Mashwani ZuR, Khan A, Laraib S, Wali R, Sarwar U. Conservation status and therapeutic potential of Saussurea lappa: an overview. Am J Plant Sci. 2017;8(3):602-14. doi: 10.4236/ajps.2017.83041.
39. Hend MT, Howayda EK, Hayat AA. Ismail and Nahla SES. Evaluation of the anti-inflammatory potential of the ethanolic extract of the Saussurea lappa root (costus) on adjuvant-induced monoarthritis in rats. J Basic Clin Physiol Pharmacol. 2015;27(1):71-8.
40. Zahara K, Tabassum S, Sabir S, Arshad M, Qureshi R, Amjad MS. A review of therapeutic potential of Saussurea lappa-An endangered plant from Himalaya. Asian Pac J Trop Med. 2014;7S1:S60-9. doi: 10.1016/S1995-7645(14)60204-2. PMID 25312191.
41. Ansari S. Ethnobotany and pharmacognosy of Qust/Kut (Saussurea lappa, CB Clarke) with special referensi of Una ni Medicine. Pharmacogn Rev. 2019;13(26):71-6.
42. Hassan R, Masoodi MH. Saussurea lappa: A comprehensive review on its pharmacological activity and phytochemistry. Curr Trad Med. 2019;5:1-11.
43. Madhavi M, Malika G, Lokanath N, Vishnu MN, Madhusudhana Chetty C, Mohamed Saleem TS. A review on phytochemical and pharmacological aspects of Saussurea lappa. Int J Rev Life Sci. 2012;2(1):24-31.
44. Choodej S, Pudhom K, Mitsunaga Tohru. Inhibition of TNF-α-induced inflammation by sesquiterpene lactones from Saussurea lappa and semi-synthetic analogues. Planta Med. 2018;84(5):329-35. doi: 10.1055/s-0043-120115, PMID 28962049.
45. Oter S, Jin S, Cucullo L, Dorman HJ. Oxidants and antioxidants: friends or foes? Oxid Antioxid Med Sci. 2012;1(1):1-4. doi: 10.5455/oams.080612.ed.001, PMID 25960927.
46. DE Flora S, Balansky R, LA Maestra S. Not available. J Prev Med Hyg. 2021;62 Suppl 3):E34-E45. doi: 10.15167/2421-4248/jpmh2021.62.1S3.1895, PMID 34622082.
47. Darenskaya M, Kolesnikova L, Kolesnikov S. The association of respiratory viruses with oxidative stress and antioxidants. Implications for the COVID-19 Ppandemic. Curr Pharm Des. 2021;27(13):1618-27. doi: 10.2174/1381612827666210222113351, PMID 33618639.
48. Aryo R, Dimas N, Rudi H. Potensi curcumin dan 4 herbal empon-empon dalam memodulasi kekebalan sel t terhadap covid-19. Herb Med J. 2021;4(3).
49. Ghada I, Abd El-Rahman, Amany AB, Nora ME, Gaber ESB, Wael NH, Dina MK, Yasmina MAE. Saussurea lappa ethanolic extract attenuates triamcinolone acetonide-induced pulmonary and splenic tissue damage in rats via modulation of oxidative stress, inflammation, and apoptosis. Antioxidants. 2020;9(5):1-23.
50. Hend MT, Howayda EK, Hayat AA Ismail, Nahla SES. Evaluation of the anti-inflammatory potential of the ethanolic extract of the Saussurea lappa root (costus) on adjuvant-induced monoarthritis in rats. J Basic Clin Physiol Pharmacol. 2016;27(1).
51. Yang X, Yang X, Kumar P, Cao B, Ma X, Li T. Social support and clinical improvement in COVID-19 positive patients in China. Nursing Outlook. 2020;68(6):830-37. doi: 10.1016/j.outlook.2020.08.008, PMID 32980152.
52. Narimane L, Tanguy D, Ouahida L, Abdeslam HM, Herve C, Chawki B, Gilles D, Hatem F, Abderrazzak B, Abdelhamid E. Nanocapsules containing Saussurea lappa essential oil: formulation, characterization, antidiabetic, Anti-Cholinesteraseanticholinesterase and anti-inflammatory potentials. Int Journal of Pharmaceutics. 2021;591:1-44.
53. Rao RN, Raju SS, Babu KS, Vadaparthi PRR. HPLC determination of costunolide as a marker of Saussurea lappa and its herbal formulation. Int J Res Pharm Chem. 2013;3(1).
54. Wahab A, Khera RA, Rehman R, Mushtaq A, Azeem MW, Rezgui M. Kuth (Saussurea lappa L.): a review of its traditional uses, phytochemistry, and pharmacological potentials. IJCBS. 2015;8:97-102.

55. Zhavoronkov A, Aladinskiy V, Zhebrak A. Potential COVID-2019 3C-like protease inhibitors designed using generative deep learning approaches. Theoretical and Computational Chemistry. 2020(2).
56. Thurakkal L, Singh S, Roy R, Kar P, Sadhukhan S, Porel M. An *in-silico* study on selected organosulfur compounds as potential drugs for SARS-CoV-2 infection via binding multiple drug targets. Chemical Physics Letters. 2021;763:1-10. doi: 10.1016/j.cplett.2020.138193.
57. Lim MA, Pranata R. Teleorthopedic: a promising option during and after the coronavirus disease 2019 (COVID-19) pandemic. Front Surg. 2020;7:10–1362. doi: 10.3389/fsurg.2020.00062, PMID 33005624.
58. Tulunay M, Aypak C, Yikilkan H, Gorpelioglu S. Herbal medicine use among patients with chronic diseases. J Intercult Ethnopharmacol. 2015;4(3):217–20. doi: 10.5455/jice.20150623090040, PMID 26401410.
59. Xian Y, Zhang J, Bian Z, Zhou H, Zhang Z, Lin Z. Bioactive natural compounds against human coronaviruses: a review and perspective. Acta Pharmaceutica Sinica B. 2020;10(7):1163-74. doi: 10.1016/j.apsb.2020.06.002, PMID 32834947.
60. Pandey MM, Rastogi S, Rawat AKS. Saussurea costus: Botanical, chemical and pharmacological review of an ayurvedic medicinal plant. J Ethnopharmacol. 2007;110(3):379-90. doi: 10.1016/j.jep.2006.12.033.
61. Taniguchi M, Kataoka T, Suzuki H, Uramoto M, Ando M, Arao K. Costunolide and dehydrocostus lactone as inhibitors of killing function of cytotoxic T lymphocytes. Biosci Biotechnol Biochem. 1995;59(11):2064-7. doi: 10.1271/bbb.59.2064, PMID 8541643.
62. Yuuya S, Hagiwara H, Suzuki T, Ando M, Yamada A, Suda K. Guanolides as immunomodulators, synthesis and biological activities of dehdydrocostus lactone, mokko lactone, eremanthin, and their dervatives. J Nat Prod. 1999;63:22-30.
63. Hamer M, Kivimäki M, Gale CR, Batty GD. Lifestyle risk factors, inflammatory mechanisms, and COVID-19 hospitalization: A community-based cohort study of 387,109 adults in UK. Brain Behav Immun. 2020;87:184-7. doi: 10.1016/j.bbi.2020.05.059, PMID 32454138.
64. Zhang L, Lin D, Sun X, Curth U, Drosten C, Sauerhering L. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors. Science. 2020;368(6489):1-8409-12. doi: 10.1126/science.abb3405, PMID 32198291.
65. Umesh, Kundu D, Selvaraj C, Singh SK, Dubey VK. Identification of new anti-nCoV drug chemical compounds from Indian spices exploiting SARS-CoV-2 main protease as target. Journal of Biomolecular Structure and Dynamics. Taylor and Francis. 2020:1-9. doi: 10.1080/07391102.2020.1763202.
66. Sindhe AM, Bodke YD, Candrashekar A. Antioxidant and *in vivo* anti-hyperglycemic activity of muntingia calabura leaves extracts. 2013;5(3):427-35.
67. Hoffmann M, Schroeder S, Kleine Weber H, Muller MA, Drosten C, Pohlmann S. Nafamostat mesylate blocks activation of SARS-CoV-2: new treatment option for COVID-19. Antimicrobial Agents and Chemotherapy. 2020;64(6):1-3. doi: 10.1128/AAC.00754-20, PMID 32312781.
68. Fukuda K, Akao S, Ohno Y, Yamashitab K, Fujiwara H. Inhibition by costunolide of phorbol ester-induced transcriptional activation of inducible nitric oxide synthase gene in a human monocyte cell line THP-1. Cancer Lett. 2001;164(1):7-13. doi: 10.1016/s0304-3835(00)00704-7, PMID 11166910.
69. Choi EM, Kim GH, Lee YS. Protective effects of dehydrocostus lactone against hydrogen peroxide-induced dysfunction and oxidative stress in osteoblastic MC3T3-E1 cells. Toxicol *in Vitro*. 2009;23(5):862-7. doi: 10.1016/j.tiv.2009.05.005, PMID 19457452.
70. Lee GI, Ha JY, Min KR, Nakagawa H, Tsurufuji S, Chang I M. Inhibitory effects of oriental herbal medicines on IL-8 induction in lipopolysaccharide-activated rat macrophages. Planta Med. 1995;61(1):26-30. doi: 10.1055/s-2006-957992, PMID 7700986.
71. Anyasor GN, Ogunwenmo KO, Oyelana OA, Akpofunure BE. Phytochemical constituents and antioxidant activities of aqueous and methanol stem extracts of Costus afer Ker Gawl. (Costaceae). Afr J Biotechnol. 2010;9:4880-4.
72. Hanan SA, Enas ND, Manal EA, Elgaffar E, Najla OA, Alnahdi HS, Danial EN, Elhalwagy MEAE, Ayaz NO. Phytochemical studies, antioxidant properties and antimicrobial activities of herbal medicinal plants costus and Cidir used in Saudi Arabia. International Journal of Pharmacology. 2017;13(5):481-7. doi: 10.3923/ijp.2017.481.487.
73. Sun J, He WT, Wang L, Lai A, Ji X, Zhai X. COVID-19: epidemiology, evolution, and cross-disciplinary perspectives. Trends Mol Med. 2020;26(5):483-95. doi: 10.1016/j.molmed.2020.02.008, PMID 32359479.
74. Narimane L, Tanguy D, Ouahida L, Abdeslam HM, Herve C, Chawki B, Gilles D, Hatem F, Abderrazzak B, Abdelhamid E. Nanocapsules containing *Saussurea lappa* essential oil: formulation, characterization, antidiabetic, Anti-Cholinesteraseanticholinesterase and anti-inflammatory potentials. Journal of Pharmaceutics. 2020;593:1-45.