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Review Article

Cetraria Islandica as a Pulmonary Cytoprotective and Supportive Herbal Remedy for Lung Complications Related to COVID-19

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Abstract

At the end of 2019, COVID-19 (SARS-CoV-2) has become a global pandemic with severe acute respiratory syndrome. The virus started from Wuhan, China on 29 December 2019 and spread widely all over the world in a short period. The present review reports the activity of one striking lichen; *Cetraria islandica* (L.) Ach. as probable complementary effective treatment for symptoms associated with Covid-19, infection. Many potential treatments have been introduced, which are considered potent antiviral drugs and commonly reported as herbal or traditional and medicinal treatments. Currently, several studies confirmed that herbal medicine plays a major role in the prevention and treatment of many diseases also for the novel coronavirus. As well as, the post-COVID syndromes which have been detected in many people who've "recovered" from COVID-19 but still suffering from its pulmonary symptoms. In the light of findings reported in the present study, *C. islandica* supplements can add a significant role to protect lung from COVID-19 symptoms and post-COVID syndrome alongside with synthetic drugs or vaccines. Therefore, *C. islandica* supplements have the potential of being utilized as novel bio-resources for naturally occurring phytotherapies.

Keywords: COVID-19, Complementary medicine, Herbal medicine, *Cetraria islandica*, Pulmonary complaints.

1. INTRODUCTION

In the future, the use of alternative plant-based molecules in the treatment of cancer, and finding new therapeutic agents with fewer side effects, both economically and because of the high side effects of existing treatments, is very important. The number of studies investigating the anticancer properties of plants is increasing day by day day (El-Darier et al., 2018 and 2021a). An in vitro study on antimicrobial and anticancer potentiality of thyme and clove oils Rendiconti Lincei. Scienze Fisiche e Naturali 29:131–139 and El-Darier, S. M., Kamal, S. A., Marzouk, R. I & Nour, I. H. (2021). Anti-Proliferative Activity of Launaea fragilis (Asso) Pau and Launaea nudicaulis (L.) Hook.F. Extracts. Biomed J Sci & Tech Res 35(2)-2021). Plants considered as a treasure of miraculous compounds with abilities to cure diseases and make our immunity strong (Li *et al*., 2019) The importance of antiviral compounds produced from plants as a traditional use is based on their wisdom, faith, availability and positive results for generations for curing ailments or diseases. Although there have been relatively few studies seeking antiviral agents from this natural source, some studies have revealed an unexpectedly frequent occurrence of antiviral activity in plants (Babich *et al.*, 2020).

Lichens can produce secondary metabolites with important biological activities such as antioxidants, antibacterial and anti-inflammatory (Sahin *et al*., 2021). Lichen extracts, could be used as the basis of some pharmaceutical formulations due to pharmacological potential of their biological active compounds especially polysaccharide content (Patriche *et al.*, 2019). Less than 100 out of 13,500 species have been investigated and polysaccharides are mainly of three different types: b-glucans, a-glucans, and galactomannans with a biological effect as antitumour, immunomodulation, antiviral, and memory-enhancing effects (Olafsdottir and Ingólfsdottir, 2001).

As well, with the global developments of COVID-19 the typical treatments must include home remedy, herbal medicine, chemical drugs, plasma therapy, and also, vaccines (Barati *et al.*, 2020). The main objective of this paper is to review the capability of *C. islandica* herbal remedy for the treatment of the lung complains associated with COVID-19 infection.

2. CORONAVIRUS (COVID-19)

WHO (2020) used the term COVID- 19 to refer to a coronavirus that affected the lower respiratory tract of patients with pneumonia in Wuhan, China. In addition, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a current reference name for COVID-19 virus. The virus belongs to the *β*-coronaviruses family which cause several symptoms related to the respiratory system. Since the beginning of the twenty-first century, three coronaviruses crossed the species barrier and causes deadly pneumonia in humans: severe acute respiratory syndrome coronavirus (SARS-CoV) (Drosten *et al.,* 2003), Middle-East respiratory syndrome coronavirus (MERS) (Zaki *et al.,* 2012), and SARS-CoV-2 (Huang *et al.,* 2020). Unlike (MERS) and (SARS), the transmission rate for COVID-19 is much higher due to the high rate of contagious and highly nonspecific symptoms of this disease (Gates, 2020).

The most thought-provoking observations that, the virus have no symptoms in some cases. While, when the virus does cause symptoms, there are common ones include fever, body ache, dry cough, fatigue, chills, headache, sore throat, loss of appetite, and loss of smell. The more interesting observation are the extreme symptoms in some cases like high fever, severe cough, and shortness of breath, which often indicates pneumonia (Huang *et al*., 2020 and Tale *et al.,* 2020).

Several natural and synthetic drugs that have antiviral activity in *vitro* were considerably less effective when tested in *vivo* conditions. It became evident that transport of the drug to cells in the infected tissue is a major difficulty, especially when tissues become inflamed as a result of the viral infection (Visintini *et al*., 2013). Since treatment of a virus infection is usually initiated when the symptoms are already obvious, introduction of a drug with antiviral activity at this stage is probably not sufficient to cure the infection if other elements such as lung, lymphocytes and connective tissues have been activated and proceed to cause damage to the virus-infected tissue. Antiviral drugs, therefore, should be used in combination with anti-inflammatory drugs to suppress both the virus and tissue effects (Perez, 2003).

Which make matters worse, the more apparent of people who've "recovered" from COVID-19 and go on to experience symptoms that linger well beyond testing negative for the virus. These individuals are sometimes referred to as "COVID long-haulers," and experts are searching for answers about this condition that's now being termed post-COVID syndrome (Tale *et al.,* 2020). Post-COVID syndrome (pneumonia pulmonary edema) can certainly impact quality of life. To overcome these prolonged pulmonary symptoms supplementary herbal medicines are effective as it's no matter for its use for long time which may be reaching to six months after recovered from the virus(El-Darier et al.,2021b).

3. LICHENS

More than 20,000 known species of lichens have been identified and inhabit diverse ecosystems ranging from arctic tundra to desert climates (Oboh and Ademosun, 2006). Ethnomedicines are a vast source of structural diversities and extensive bioactivities that can serve as a huge source of potential antiviral drugs. A significant number of plants serve as potential remedies to decrease the severity of illness caused by viruses (Jadhav *et al*., 2012). Lichen is a stable, ecologically obligate, composite organism that emerges from an exhibiting fungus (the mycobiont) and one or more extracellularly located photoautotrophic unicellular or filamentous algal species (Hawksworth and Honegger, 1994). So that, there is a self-supporting mutualism between algae or cyanobacteria and the fungi as a beneficial symbiotic relationship.

It has been observed that the medical importance of the lichens has increased with secondary metabolites that they produce (Sahin *et al*., 2019). Secondary metabolites have been shown to have anticancer (Emsen *et al*., 2021), gastroprotective (de Castro Fonseca *et al*., 2016), antinociceptive (Melo *et al*., 2008), antibacterial (Gökalsın and Sesal, 2016), antifungal (Karabulut and Ozturk, 2015), antiviral (Sokolov *et al*., 2012), antiprotozoal (Schmeda-Hirschmann *et al*., 2008), and insecticidal (Emsen *et al*., 2015) properties. Interestingly, it was found that lichens are effective in the treatment of bronchitis and tuberculosis diseases (Kim and Choc, 2007). So as to lichens may be considered as an easily accessible sources of natural drugs and possible food supplements after their safety evaluations (Turkez *et al*., 2012). Their biological activities and chemical compositions have long been investigated for their anti-microbial (Candan *et al*., 2007), antiviral (Fazio *et al*., 2007) and anti-tumor effects (Rezanka and Dembitsky, 2006). From these purposes, Lichens are used in folk medicine for the treatment of diverse pathologies, from respiratory to digestive diseases, as they contain over 500 potentially bioactive compounds identified up-to-date.

Secondary metabolites are produced by the fungus alone and secreted onto the surface of lichen's hyphae either in amorphous forms or as crystals. If these substances are only found in lichens, they are called lichen substances (Öztürk *et al*., 1999). One of the most specific lichen substances is lichenic acids, such as usnic acid, lobar acid, lecanoric acid or salazinic acid, are among these compounds, with biopharmaceutical applications as antimicrobial, antioxidant and cytotoxic agents.

3. 1 *CETRARIA ISLANDICA* (L.) ACH.

3.1.1Morphology

Cetraria islandica (Iceland moss, Parmeliaceae) is lichen whose erect leaf like habit gives it the appearance of a moss, where its name comes (Plate 1).

Plate-1: Morphology of *Cetraria islandica*.

Cetraria islandica vary in colour from deep brown to grayish white and may grow to a height of 7 cm. It is the first lichen used as food by humans (HMPC, 2017).

3.1.2 Medicinal uses

Cetraria islandica has been used through the ages in traditional medicine in many countries. It was supposed to be effective in treatment of pulmonary tuberculosis, throat irritation, gastritis, dry cough, diabetes, hemorrhoids, bronchitis and dysentery. It is a cooling expectorant, soothes irritated tissue and controls vomiting. Traditionally, it is used mild inflammation of the oral and pharyngeal mucosa. It is also valued in dyspepsia and loss of appetite. It stimulates the secretion of saliva and gastric juices. *Cetraria islandica* is one of nature's most potent cough relievers; it is a well-known sore throat remedy and a fantastically in tackling all kinds of respiratory problems such as treatment of pulmonary tuberculosis. The lichen has valued folk remedy for lung diseases, kidney and bladder complaints as well as externally for poorly healed wounds (Bown, 2001).

Cetraria islandica neither has toxic effects nor do drug interactions by its use as a supplement remedy (Patriche *et al*., 2019). Freysdóttir *et al.* (2008) suggested that the aqueous extract from *C. islandica* has an anti-inflammatory effect and protolichesterinic acid was found to be a potent inhibitor of the DNA polymerase activity of human immunodeficiency virus (HIV), with 50% inhibitory dose of 24 µM. It is not cytotoxic with cultured mammalian cells (Güven *et al*., 2018). Furthermore, Gulcin *et al.* (2002) study the antioxidant activity of *C. islandica* and obtained that the aqueous extract of *C. islandica* can be used as an easily accessible source of natural antioxidants as a possible food supplement or in pharmaceutical industry. The historical overview of the important medicinal uses of *C. islandica* indicates that there are specific chemical constituents such as high proportions of polysaccharides lichenan and isolichenan, galactomannans, glucans and several secondary metabolites such as protolichesterinic acid and fumarprotocetraric acid, lichenolic acids and aliphatic lichen acid (Olafsdottir and Ingólfsdottir, 2001).

3.1.3 Active constituents

A. Polysaccharides

β-glucan lichenan

Isolichenan (a (1,3;1,4)-linked β-glucan) is present along with lichenan (Kramer *et al.*, 1995). The first polysaccharide fraction isolated from *C. islandica* was a mixture of lichenan and isolichenan in 1813 by Berzelius (smith, 1921). The (1,3;1,4)-β-glucan lichenin is extractable with hot water from the fronds of *C. islandica*. The glucan is located in the cell walls of the mycobiont (Honegger and Haisch, 2001) and exhibited antiviral activity against numerous viruses of different taxonomic groups (TMV, PVY, TEV, PYX, TRV, CMV) (Stübler and Buchenauer, 1993).

McCarty and DiNicolantonio (2020) recently described the potential role of β glucan as a natural nutraceutical for boosting type 1 interferon response to RNA viruses such as influenza and coronavirus. Putative use of β-glucans in mitigating lung infections correlates with findings from our recent in vivo studies to address ARDS (Masterson *et al.*, 2019).

Galactomannans

Galactose and mannose were recognized early 1906 as a polysaccharide fractions extracted from *C. islandica* (Ulander *et al.*,1906) but more detailed structural investigations on this group of lichen polysaccharides were mainly carried out over the past 15 years. These polysaccharides have a strong antiviral activity. As well as sulfate derivative, GE-3-S, prepared

by chlorosulfonic acid treatment of GE-3 has been shown to inhibit the replication of human immunodeficiency virus (HIV) in vitro. GE-3-S inhibited the cytopathic effect of HIV and suppressed HIV-antigen expression in Molt-4 cells without inhibiting HIV-reverse transcriptase. Sulfate derivatives of lichenan from *C. islandica* and PC-3 from *Parmelia caperata* were inactive against HIV as were the unsulfated counterparts (Hirabayashi *et al.*, 1989).

B. Lichen acids

Cetraria islandica contains large amounts of fumaroprotocetraric acid (2.6-11.5%) and protocetraric acid (0.2-0.3%) with strong antioxidant and bacteriostatic effects. Lichen acids and fumaric acid considered as immunomodulatory as they dominate the immune system and regulate the immune response. Isolated protolichesterinic acid was found to be a potent inhibitor of the DNA polymerase activity of human immunodeficiency virus-1 reverse transcriptase (HIV-1 RT), with 50% inhibitory dose of 24 µM. It showed negligible cytotoxic activity with a variety of cultured mammalian cells (Pengsuparp *et al.*, 1995). Virus inhibition is more likely the result of suppressive effects on virus replication or cell-to-cell movement from initially occupied cells (Stübler and Buchenauer, 1996).

3. CONCLUSION

In the light of findings reported in the present study, *C. islandica* supplements can add a significant role to protect lung from COVID-19 symptoms and post-COVID syndrome alongside with synthetic drugs or vaccines. Therefore, *C. islandica* supplements have the potential of being utilized as novel bio-resources for naturally occurring phytotherapies.

4. RECOMMENDATIONS

Herbal tea of *C. islandica* was recommended as a demulcent for the symptomatic treatment of oral or pharyngeal irritation, lung complaints as well as associated dry cough (Herbal tea: 1.5 g of the comminuted herbal substance in 150 ml of boiling water as an herbal infusion or as a macerate 3 to 4 times daily). Enhancement of immunity system was acquired from 2 g of the *C. islandica* substance boiled in 100 ml water for 15 minutes.

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