

RESEARCH ON VIETNAMESE MEDICINAL PLANTS WITH POTENTIAL IN THE TREATMENT OF COVID-19 DISEASE

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Abstract:

Natural products have been considered the primary source of healthcare among the majority of the world's population. In the therapeutic management of Covid-19, products of natural origin are a promising and potential medicinal source to treat this disease. Our research methodology is based on a review of recent articles reporting on the effect of medicinal plants on Covid-19. In this review, literature searches on medicinal plants which used to treat and prevent Covid-19 disease were conducted. From this research, several medicinal plants have received much research attention such as *Astragalus mongholicus* Bunge; *Astragalus membranaceus* (Fisch.) Bunge; *Atractylodes lancea* (Thunb.) DC.; *Atractylodes chinensis* (DC.) Koidz.; *Atractylodes japonica* Koidz.; and *Atractylodes macrocephala* Koidz.; *Andrographis paniculata*; *Lonicera japonica*; *Scutellaria baicalensis* Georgi. However, the definitive roles of these medicinal plants in cytokine storms and post-infection complications still need further investigation. And then, quality control and standardisation of medicinal plants-based products also need to be emphasized. Further investigations on differential effects as well as the quality and safety of herbal medicines should be required to ascertain their role in Covid-19 therapeutic management. Furthermore, herbal mixtures, medicinal plants, natural products, or their combination with possible anti-SARS-CoV-2 effects may hold promise and effectiveness in preventive and therapeutic support for Covid-19.

Keywords: Covid-19; Coronavirus; Research on medicinal plants.

1. Introduction

Covid-19 is a viral infectious disease that causes severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2). The disease first appeared in Wuhan (China) in December 2019. This world pandemic has caused millions of infections and thousands of deaths around the world (Huang et al. 2020). The virus is known to spread from bat to human and humans through respiratory droplets produced during coughing or sneezing. Common symptoms of this disease included myalgia, fatigue, fever, cough,

shortness of breath, and breathing difficulties. Moreover, the infection can cause pneumonia, diarrhea, nausea-vomiting, headache, hemoptysis, severe acute respiratory syndrome, kidney failure, and even death (Joshi et al. 2020). The period from incubation to symptoms onset maybe range from 2 to 14 days or even longer. Cytokine-release syndrome (CRS), informally called “cytokine storm”, often occurs in SARS-CoV-2 infection because of the massive release of inflammatory cytokines due to multiple organ failures. Abnormal levels of cytokines and

chemokines (IL-1, IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, IL-13, IL-17, M-CSF, G-CSF, GM-CSF, IP-10, IFN- γ , MCP-1, MIP-1 α and TNF- α) are found in Covid-19 patients. Furthermore, vascular endothelial growth factors (VEGF), especially IL-12, IL-7, IL-10, G-CSF, IP-10, MIP-1 α , MCP-1, and TNF- α are also significantly increased. This finding of CRS induced by SARS-CoV-2 infection was helpful in that it has guided clinicians to focus on immuno-modulatory therapies for this infection. Unfortunately, till now, there are no specific therapies for Covid-19, but preventive and supportive treatments are suggested to control further complications by the use of drugs such as hydroxychloroquine, chloroquine, lopiravir, ritonavir, remdesivir, azithromycin,... and coupled the supportive care as oxygen therapy, fluid management,... (Hoffmann et al., 2020). Covid-19 has become a challenging pandemic for the whole world because of its impact on social structures, health infrastructures, and healthcare,... Therefore, all resources must be mobilized against Covid-19 including traditional medicine. A few countries such as China and India with a long history of traditional medicine have tried to explore the role of traditional and complementary in the search for an effective treatment or drug. Vietnam with the potential of a tropical country with a rich and diverse source of medicinal plants has always been interested in the use of medicinal plants and traditional medical knowledge in healthcare. In attempts to curb the disease spread, the Ministry of Health has issued a lot of guidelines on the use of traditional remedies, medicinal herbs, herbal products, and supplements,... for the treatment and prevention of Covid-19.

In this review, we focus on the possible uses of herbal traditional medicines and natural products in the prevention and treatment of Covid-19 infection.

2. Research overview

Natural products have been considered the primary source of healthcare among the majority of the world's population. In the management of Covid-19, natural products are a promising and potential source of treatment for this disease. Several methods using

medicinal plants were also recommended for the prevention of Covid-19. About fifteen medicinal plants have been highlighted that could prevent or be used as an alternative treatment for Covid-19 patients (Liu et al., 2020). It has been well reported that natural products contain various types of phytochemicals including alkaloids, flavonoids, phenolic compounds, glycosides, and tannins with potential effects that promote immune response, as well as prevent viral replication (Klos et al., 2009). In another review, fifteen medicinal plants with natural products tested against coronaviruses and eleven medicinal species and mixtures with possible anti-SARS-Covid-2 effects have been documented (Benarba et al., 2020). This review showed that only one study investigated the antiviral activity against SARS-CoV-2 and another on the human coronavirus NL63, while the other were not cell-based. Most of the research is conducted toward the isolation of natural compounds and testing of their biological activity with *in vitro* and *in vivo* experiments. As a result, knowledge of natural products used to treat Covid-19 is limited and not well documented.

3. Methodology

Our research method is based on a review of recent articles reporting on the effect of medicinal plants on Covid-19. The literature search has been conducted for medicinal plants which used to treat and prevent Covid-19 disease as well as the results of the *in vitro* evaluations and recognition of the natural compounds and their antiviral activity. From April to July 2022, this research has been conducted on electronic databases such as PubMed, Web of Science, and Google Scholar, as well as hand-searching of literature including books on herbal and traditional medicine available in the library's resources. The search terms used are "Covid-19", "antiviral", "anti-inflammatory", "immunomodulatory", "safety", and "toxicity".

4. Result

From this our research method, several medicinal plants have received much research attention such as *Astragalus mongholicus* Bunge; *Astragalus membranaceus* (Fisch.)

Bunge; *Atractylodes lancea* (Thunb.) DC.; *Atractylodes chinensis* (DC.) Koidz.; *Atractylodes japonica* Koidz.; and *Atractylodes macrocephala* Koidz.; *Andrographis paniculata*; *Lonicera japonica*; *Scutellaria baicalensis* Georgi.

4.1. *Astragalus*

Astragalus is the largest genera of flowering plants with over 1,750 species. The two botanical sources used in traditional medicine with the Latin name *Radix Astragali* are *Astragalus mongholicus* Bunge and *Astragalus membranaceus* (Fisch.) Bunge. *Astragalus* acted as regulated blood (vital energy), invigorating the body fluids, preparing the flow of blood to fight against the attack of external evils (pathogens), and strengthening body defenses, which regulates blood exhaustion and is mainly used to treat syndromes of various “blood deficiencies” in spleen, stomach, and lungs. *Radix Astragali* has been recommended for use in the treatment of SARS-CoV infection by The Ministry of Health of Vietnam. A recent study reported that aqueous root *Astragali radix* extract presents their biological activity through the stimulatory effect on cell proliferation and the enhance IL-1 α and IL-12 expression (Gong et al., 2018). And *Radix Astragali* also enhanced the metabolic syndrome in the kidney of rats through the angiotensin-converting enzyme 2 (ACE2). The expression of ACE2 mRNA decreased in the kidney of a rat which explained that *Radix Astragali* dose-dependently increased the expression of ACE2 in the rat kidney (Yan et al., 2009).

4.2. *Atractylodes*

Genus *Atractylodes* is the main source of *Atractylodis Rhizoma* – one of the ingredients in traditional medicine formula used for the treatment of Covid-19 in China and Vietnam. This genus comprises eight species including *Atractylodes lancea* (Thunb.) DC. (*A. lancea*), *Atractylodes chinensis* (DC.) Koidz. (*A. chinensis*), *Atractylodes japonica* Koidz. (*A. japonica*), and *Atractylodes macrocephala* Koidz. (*A. macrocephala*) etc. Dried rhizomes of *Atractylodes* plants have been used for hundreds of years for invigorating the spleen and eliminating dampness. *Atractylodenolide-III*

(ATL-III) has been known as the major component of *Atractylodes rhizome*. A previous study showed that ATL-III inhibited the production of pro-inflammatory cytokines, such as IL-6, IL-1 β , TNF- α , and IL-8 (Yoo et al., 2017). Furthermore, ATL-III can reduce chronic kidney disease-induced inflammation and muscle atrophy by inhibiting the PI3K-Akt pathway (Wang et al., 2019). And then, ATL-III also reduces the production of proinflammatory mediators NO, reduces the levels of TNF and IL, and then relieves the damage to renal cells (Ishii et al., 2020). Therefore, rhizoma *Atractylodis* has been used for clinical prevention and treatment of renal injury after Covid-19 infection (He et al., 2020).

4.3. *Andrographis*

Andrographis paniculata, a familiar traditional medicine, has been approved for use in Covid-19 treatment by the Ministry of Health of Vietnam. *A. paniculata* is an herbal remedy used as a bitter tonic to treat diarrhea, and malaria, to relieve symptoms of common colds and upper respiratory tract infections. A recent review compiled previous literature on the evaluation of evidence for the Covid-19 antiviral by *A. paniculata* (Lim et al., 2021). Their *in silico* and *in vitro* studies collectively suggested multi-pathway targeting SARS-CoV-2 antiviral properties of andrographolide and its analogs including the spike protein-ACE-2 receptor complex, spike protein, ACE-2 receptor, RdRp, 3CL^{pro}, PL^{pro}, and N-protein RNA-binding domain. Another study has evaluated the anti-SARS-CoV-2 activity in Calu-3 cells of *A. paniculata* extract and its major component, andrographolide. Postinfection treatment of *A. paniculata* and andrographolide in SARS-CoV-2-infected Calu-3 cells significantly inhibited the production of infectious virions with an IC₅₀ of 0.036 μ g/mL and 0.034 μ M, respectively, as determined by the plaque assay (Sa-Ngiamsumtorn et al., 2021).

4.4. *Scutellaria*

Scutellaria baicalensis Georgi. a species in the genus *Scutellaria* (family Lamiaceae) has long been used in traditional medicine for heat-clearing, fire purging, detoxification, and hemostasis. The extracts of *S. baicalensis* have

exhibited a broad spectrum of anti-viral activities including ZIKA (Oo et al., 2019), H1N1 [Ji et al., 2015], and HIV (Zhang et al., 1991), DENV (Zandi et al., 2013). The ethanol extract of *S. baicalensis* and its major component, baicalein, inhibit SARS-CoV-2 3CL^{pro} activity *in vitro* with IC₅₀'s of 8.52 µg/mL and 0.39 µM, respectively. Both of them inhibit the replication of SARS-CoV-2 in Vero cells with EC₅₀'s of 0.74 µg/mL and 2.9 µM, respectively [Liu et al., 2021]. The most active ingredient of *S. baicalensis* is baicalin (7-D-Glucuronic Acid-5,6-Dihydroxyflavone). It can directly inhibit SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) activity and exhibit significant antiviral activity against SARS-CoV-2 *in vitro* ([Zandi et al., 2021]. Moreover, it was reported that baicalin can suppress angiotensin-converting enzyme 2 (ACE2) activity to inhibit the attachment of SARS-CoV spike protein (S-protein) to ACE2, which was the entrance of SARS-CoV-2 into host cells *via* S-protein, reducing infections (Yang et al., 2020; Boozari and Hosseinzadeh, 2021). In influenza A-infected A549 and MDCK cells, baicalin also could increase IFN levels, resulting in a reduction of pro-inflammatory cytokines production (Nayak et al., 2014). Meanwhile, baicalin greatly attenuated inflammatory cell infiltration and decreased the levels of pro-inflammatory cytokines tumor necrosis factor α (TNF- α), IL-6, and IL-1 β by regulating a variety of molecular mechanisms including Nuclear erythroid factor 2 (Nrf2)/heme oxygenase 1 (HO-1), CX3CL1-CX3CR1 axis and TLR4/MAPKs/NF- κ B, to defend against lipopolysaccharide-induced severe lung injury [Ding et al., 2016; Meng et al., 2019; Long et al., 2020]. Baicalin also boosted the differentiation and modulatory activity of Foxp3⁺ Treg cells, promoted TGF- β secretion, and significantly inhibited the production of inflammatory cytokines (Yang et al., 2019). The previous study also presented positive features of multi-pathway and multi-target effects of baicalin to inhibit cytokine storm and initially unveiled the mechanism of baicalin in inhibiting cytokine storm through the TNF signaling pathway (You et al., 2022).

4.5. *Lonicerae*

Lonicera is an important genus of the family Caprifoliaceae, including over 200 species. *Lonicera japonica* is the most common species used and studied plant of the genus *Lonicera*. Apart from the flower buds, the other parts of *L. japonica* including roots, stem barks, leaves, fruits, and whole plants, are also used for traditional medicinal materials. The flower or dry bud of *L. japonica* is traditionally used as an anti-inflammatory herb, and it is efficacious for treating various viral infections, such as hepatitis B virus (Ge et al., 2017), influenza A virus (Ding et al., 2017), dengue virus (Lee et al., 2017), and respiratory syncytial virus (Lee et al., 2021). A previous study demonstrates that the extract of *L. japonica* significantly inhibited SARS-CoV-2 virus replication (Zhou et al., 2020) and effectively protected the effect against mild Covid-19 by regulating a complex molecular network (Li et al., 2021). It also accelerated the negative conversion of infected patients (Zhou et al., 2020). Another study reported that the extracts of *Lonicera japonica* and *Astragalus membranaceus* have been upregulated by a group of microRNAs including let-7a, miR-148b, and miR-146a, which are critical to reducing the pathogenesis of SARS-CoV-2. Moreover, these herbs suppressed pro-inflammatory cytokines including IL-6 and TNF- α , which were both identified in the cytokine storm of acute respiratory distress syndrome, a major cause of Covid-19 death. Furthermore, both herbs partially inhibited the fusion of SARS-CoV-2 spike protein-transfected BHK-21 cells with the human lung cancer cell line Calu-3 that was expressing ACE2 receptors. These herbs inhibited SARS-CoV-2 M^{pro} activity, thereby alleviating viral entry as well as replication (Yeh et al., 2022).

5. Discussion

Several medicinal plants that have recently received attention have been reported in this review such as *Astragalus mongholicus* Bunge; *Astragalus membranaceus* (Fisch.) Bunge; *Atractylodes lancea* (Thunb.) DC.; *Atractylodes chinensis* (DC.) Koidz.; *Atractylodes japonica* Koidz.; and *Atractylodes macrocephala* Koidz.; *Andrographis paniculata*; *Lonicera japonica*;

Scutellaria baicalensis Georgi. Among the medicinal plants reviewed here, it appears that the *Scutellaria baicalensis* Georgi may be a promising therapeutic drug for the treatment of Covid-19. Several researchers have reported that baicalein - the major component of the *Scutellaria baicalensis* Georgi and its analog (Baicalin) have presented their potential as broad spectrum anti-CoV agents in both *in vitro* and *in vivo* experiments. However, the anti-SARS-CoV-2 activity induced by the baicalein and its analog needs to be evaluated in detail in further study.

Currently, at the same time as the vaccination of the entire population, the search for medicinal plants and medicinal plant-based therapeutics is ongoing, especially in middle and low-income countries. However, the definitive roles of these medicinal plants in cytokine storms and post-infection complications remain to be further investigated. And then, quality control and standardisation of medicinal plants-based products also need to be emphasized. Various phytochemicals in the plants have exhibited multimodal mechanisms of action, ethanol, methanol, and acetone extracts also reported anti-inflammatory activity in laboratory animals *via* modulation of levels of inflammatory cytokines and mediators including the pro-inflammatory (NF κ B, TNF- α , IL-1 β , IL-6, IL-8, NO, CRP) and anti-inflammatory markers associated with severe disease likely related to cytokine storm (Ding et al., 2016; Meng et al., 2019; Long et al., 2020; You et al., 2022; Yeh et al., 2022). However, these studies are still very limited. And, the document safety records of the medicinal plants-based are still insufficient. Several animal toxicity studies have reported variable adverse effects including arrhythmia, hypoglycemia, and blood pressure reduction at high doses (Koley and Lal, 1994; Hore et al., 1999). This can be explained by the diversity and complexity of phytochemical and

bioactivity compounds in medicinal plants and natural products. Therefore, the quality control process to meet stringent regulatory standards of safety considerations is time-consuming and lengthy. That is one of the main challenges of phytopharmaceutical development for the therapeutic claim is quality control, identification, and standardisation of bioactive compounds of plant-based products. However, in the face of these challenges, medicinal plants research should still be studied and considered during Covid-19 pandemic.

6. Conclusion

Medicinal plants and natural products are still considered promising alternatives to prevent or treat several diseases as well as Covid-19 infection. There are various traditional herbal medicines used and resulted in positive health effects among Covid-19 patients. In the present review, some medicinal plants discussed here can potentially provide a multimodal approach via antiviral, anti-inflammatory, and immunomodulatory effects in Covid-19 management. At present, it is challenging to pool data from published studies due to variation in extracts selection, research methodology, and a lack of well-reported standardisation data of the investigated. Nevertheless, several limitations have been detected concerning the specificity of the action exerted by such products, sustainable sourcing of the species, doses range used, or the use of appropriate controls. Still, it is quite clear that there is insufficient evidence of direct antiviral effects specific to the SARS-CoV-2. Further investigations on differential effects as well as the quality and safety of herbal medicines are required to ascertain their role in Covid-19 management. Furthermore, herbal mixtures, medicinal plants, natural products, or their combination with possible anti-SARS-CoV-2 effects may be promising preventive and therapeutic alternatives Covid-19.

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CÁC NGHIÊN CỨU VỀ CÂY THUỐC Ở VIỆT NAM CÓ TIỀM NĂNG TRONG HỖ TRỢ ĐIỀU TRỊ COVID-19

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Tóm tắt: Các sản phẩm có nguồn gốc tự nhiên được coi là nguồn chăm sóc sức khỏe chính của phần lớn dân số thế giới. Trong việc điều trị Covid-19, các sản phẩm có nguồn gốc tự nhiên là một nguồn đầy hứa hẹn và tiềm năng để điều trị căn bệnh này. Phương pháp nghiên cứu của chúng tôi dựa trên xem xét các bài báo gần đây báo cáo về tác dụng của cây thuốc đối với Covid-19. Trong bài báo này, chúng tôi đã tiến hành tìm kiếm tài liệu về các loại cây thuốc được sử dụng để điều trị và phòng ngừa bệnh Covid-19. Từ những tìm kiếm này, một số cây thuốc đang được quan tâm nghiên cứu gồm: *Astragalus mongholicus* Bunge; *Astragalus membranaceus* (Fisch.) Bunge; *Atractylodes lancea* (Thunb.) DC.; *Atractylodes chinensis* (DC.) Koidz.; *Atractylodes japonica* Koidz.; and *Atractylodes macrocephala* Koidz.; *Andrographis paniculata*; *Lonicera japonica*; *Scutellaria baicalensis* Georgi. Tuy nhiên, vai trò chính xác của những cây thuốc này trong cơ chế con báo cytokine và các biến chứng nặng vẫn cần nghiên cứu thêm. Sau đó, việc kiểm soát chất lượng và tiêu chuẩn hóa các sản phẩm tự nhiên cần được thực hiện. Cần có các nghiên cứu sâu hơn về tác dụng khác nhau cũng như chất lượng và độ an toàn của thuốc được liệu để xác định chính xác vai trò của nó trong việc hỗ trợ điều trị Covid-19. Việc sử dụng cây thuốc, sản phẩm tự nhiên và sự kết hợp của chúng với các tác dụng chống virus SARS-CoV-2 mang lại nhiều hứa hẹn và hiệu quả trong hỗ trợ phòng ngừa và điều trị Covid-19.

Từ khóa: Covid-19; Coronarivirus; Các nghiên cứu về cây thuốc.