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Medicinal plants and the communication on precautionary use of herbs during COVID-19 outbreak in Thailand

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ABSTRACT

COVID-19 has become a new global health issue that spreads easily and has high mortality rates across the world. Consequently, it is essential to discover new treatments rapidly. According to Integrative Medicine, certain herbs are useful for treating COVID-19 when taken with standard treatments. Thailand is one of the countries experiencing outbreaks and treating patients with herbs. For instance, some Thai patients are treated with Fah Talai Jone (*Andrographis paniculata*) at a different quantity limit used for treating fever and sore throats. Fah Talai Jone must be used with high precaution in renal insufficiency, hepatitis, or drug induced liver damage patients. In addition, finger root (*Boesenbergia rotunda)* and ginger (*Zingiber officinale)* are also used for managing COVID-19, but there is insufficient evidence about quantity limits and side effects of using them. Therefore, specialists need to do more research about the herbs to ensure the efficiency and safety of treatments.

Keywords: herb in COVID, Fah Talai Jone, andrographolide, finger root, ginger, COVID, herb communication

INTRODUCTION

The COVID-19 outbreak has spread in Thailand since 2020. The disease is caused by a newly discovered strain of coronavirus, called SARS-CoV2 by the Coronaviridae study group (CSG) of the International Committee on Taxonomy of Viruses (ICTV) [1]. The World Health Organization (WHO) has renamed the virus as Coronavirus Disease-2019 (COVID-19) and considers it as a virus affecting the respiratory system. In addition, it can result in severe respiratory symptoms of patients with weak immunity. The inflammation and cytokine storm caused by the virus could fatally damage the lungs and other respiratory organs; the patients will have acute respiratory failure [2-3]. Herbs are one of the alternative medicines that patients can access and use to promote health and wellness [4]. In Thailand, there are many herbs and traditional medical drugs used to manage fever and sore throat symptoms [5-6]. Some of the Thai people want to use herbs for symptom management but need more information and communication from healthcare practitioners.

Fah Talai Jone is the herb used for managing sore throat, fever and diarrhea in Thailand [7]. It has been used for a long time in traditional medicine. During the flu pandemic, the Thai people believed Fah Talai Jone could help with symptom management, but did not mention the dose of andrographolide in Fah Talai Jone[7-8]. Physicians have many concerns about the safety and drug interactions of Fah Talai Jone, but Thai traditional medicine and the Thai people believe in using it to manage flu, sore throat, and fever symptoms. Thus, there needs to be more research and information about the pharmacological actions, precautions, drug-drug interactions and allergy profile of Fah Talai Jone, especially in terms of pandemics. Communication between health practitioners and patients about safety and drug interaction is very important and should be introduced while educating patients about herbs.

COVID-19 Patho-Physiology: Coronavirus is regarded as an RNA enveloped virus (the RNA of the virus is contained within an envelope). The structure consists of Spike (S) glycoprotein, small envelope (E) protein, matrix (M) protein and nucleocapsid (N) protein, and RNA genome. The virus enters the host cells through angiotensin- converting enzyme 2 (ACE2), which is mostly located in respiratory organs and digestive tracts [9]. As a result, the symptoms typically begin with cough and fever. Furthermore, when the virus enters the bloodstream via the lungs, called viremia, a virus will have access to organs with ACE2 receptors, such as the heart, kidneys, and brain [10]. Once the virus binds with receptors in the organs, it is mediated by transmembrane serine protease 2 (TMPRSS2), which allows it to enter cells and produce multiple copies of themselves. The process triggers the body to mount an inflammatory response, signaling white blood cells such as dendritic cells, macrophages, and T-cells. The cells then heal the body and defend against the viruses. However, if the cells could not fight against the pathogens, there would be severe inflammation, which will mortally damage pulmonary tissues. In severe cases, there would be the hyperproductions of IL-6, IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (G- CSF), monocyte chemoattractant protein-1 (MCP1), IFNγ, macrophage inflammatory protein 1α (MIP1α), and tumor necrosis factor (TNF) [11], resulting in a cytokine storm. However, cell biology, molecular

biology, and immunology could help develop medicines and lessen the development of severe COVID by providing more knowledge about viruses and phytochemicals.

Drug use in COVID-19 virus infection: The patho-physiological data of the virus helps develop medicines for COVID-19 treatments. The drugs may be classified by mechanisms of action as 1. Viral replication inhibitor, such as ribavirin, remdesivir, favipiravir, emtricitabine/tenofovir, and oseltamivir; 2. Viral protease inhibitor, including lopinavir/ritonavir, darunavir, danoprevir, and atazanavir; 3. Viral entry inhibitor, such as hydroxychloroquine, umifenovir, baricitinib, bromhexine; 4. Anti- inflammatory agent, including tocilizumab, sarilumab, and steroids drug, etc. [9-11]. However, some available drugs had to be repurposed to treat COVID-19, since the disease is newly emergent. Furthermore, prescription medications in each country depend on their ability to access the medications. Some Thai patients take supplements, vitamins, and herbs along with their medical treatments. Consequently, physicians have to carefully consider drug interactions because the drugs might prevent the other drugs from performing effectively or induce a serious adverse reaction.

Herbal medicine for COVID-19 infection: The field of alternative medicine continues to study herbs and their effectiveness for treating COVID-19. Accordingly, the Thai government started to treat patients with herbs, allowing numerous patients rapid access to medications. On the other hand, most studies about herbs are conducted in laboratory (*in vitro*), and some of these medicinal-herbs have various side effects, such as increased risk of kidney and liver damage. Carelessly taking herbs can be dangerous for patients. As a result, only Thai traditional medicine physicians have the authority to prescribe herbal medicine. Most of the provided medicines are prepared with the Thai Herbal Pharmacopoeia rather than using only a single type of herbs.

Andrographis paniculate: *Andrographis paniculata* is called “Fah Talai Jone” in Thai, and is also known as the king of bitters because of its taste. Fah Talai Jone is shown in Figure 1. The leaves and shoots of the plant are used for developing medicines. According to Thai local medicine, leaves are pulverized and mixed with honey in order to treat the flu and sore throat. Fah Talai Jone contains a bioactive compound called lactone compound, which consists of andrographolide, neoandrographolide, 14-deoxy-11, 12-didehydroandrographolide, and 14-deoxyandrographolide. According to the Thai Herbal Pharmacopoeia, Fah Talai Jone medicine approved by the Thai FDA must contain no less than 6% w/w lactone compound and at least 1% w/w andrographolide [12]. Since Fah Talai Jone medicine is considered an over the counter medicine for treating the common cold, sore throat, and non-infectious diarrhea, it is freely available in pharmacies and convenience stores. It can be sold in numerous forms including tablet, capsule, and powder extract.

Figure 1. The flower and leaves of *Andrographis paniculate* or Fah Talai Jone.

Severe acute respiratory syndrome coronavirus-2 led researchers to again study the benefits of herbs. First, they studied an *in-silico* model to check molecular docking results. As a result, it was evident that Fah Talai Jone is effective in suppressing the virus by forecasting the binding structure of SARS-CoV-2 Mpro, S-spike protein, ACE2 receptor, RdRp, and N-protein RNA-binding domain. It was found out that the herb might be able to bind with viruses in many positions [13-17] and fight against them. Subsequently, Sangiamsuntorn K, et al. tested Fah Talai Jone with infected human lung epithelial cells (Calu-3). The results indicated that both Fah Talai Jone extract and andrographolide have an ability to inhibit the COVID-19 infections. Fah Talai Jone extract contains 9.54 μg/ml of IC50, while andrographolide contains 1.68 μM. By plaque assay, it was observed that both could work against the new coronavirus with dose-dependent metabolism. The IC50 of Fah Talai Jone extract was 0.036 μg/ml and that of andrographolide was 0.034 μM [18]. Nonetheless, they were not proven to be useful for prevention. Afterwards, 6 COVID-19 infected patients with mild symptoms were given 3 andrographolide 20 mg capsules 3 times per day for 5 days (andrographolide 180 mg per day). On days 3 and 5, the patients' symptoms decreased, but one had an increase in liver enzyme, exceeding the normal. Next, the medicines were tested in 309 patients. The results showed that 306 recovered very well in 5 days. The others experienced pneumonia, less than that of those who did not take herbal medicines. Consequently, the Department of Thai Traditional and Alternative Medicine planned to do further research [12]. Moreover, Fah Takai Jone was found to have anti-microbial and anti-viral effects and is effective against the common cold [19]. Given these results, the Thai Ministry of Public Health decided to allow asymptomatic patients to take Fah Talai Jone medicines with 60 mg of andrographolide 3 times per

day (andrographolide 20 mg per meal) for 5 days. For mild symptomatic patients, they recommended taking Fah Talai Jone medicines with 180 mg of andrographolide 3 times per day for 5 days [20]. However, children, pregnant and breastfeeding women, and people allergic to Fah Talai Jone are not recommended to take these medicines; even if they have severe COVID-19 symptoms, they must receive standard treatment. The use of anti-hypertensive drugs and anti-coagulant drug, such as warfarin, clopidogrel, aspirin could cause synergism of drugs. Additionally, Fah Talai Jone could inhibit cytochrome P450: CYP1A2, CYP2C9, CYP3A4, which is involved in the metabolism of some drugs. Therefore, Fah Talai Jone might affect liver enzymes, weakened muscles, and other symptoms including vomiting, diarrhea, nausea, fatigue, and low appetite. [19-21]

Boesenbergia rotunda: Finger root, shown in Figure 2, is used as a Thai food ingredient. It has a specific spiciness and fragrance, and its rhizome is used for medicines. It consists of many bioactive compounds, such as 5- Hydroxy-7-methoxyflavanone (Pinostrobin), 5,7-Dihydroxyflavanone (Pinocembrin), 2',6'-Dihydroxy-4'-methoxychalcone (Pinostrobin chalcone), Boesenbergin, Camphor, Linalool, and Panduratin A. , The Panduratin A in Vero E6 cells has potent anti SARS-CoV-2 activity with an IC50 of 3.62 μg/ml (CC50 = 28.06 μg/ml), and can inhibit SARS-CoV-2 infection at the both pre-entry and post infection phases [22]. Additionally, the ethanol found in finger root can inhibit other viruses, such as Foot and Mouth Disease Virus (FMDV) type O and Dengue virus. Other components, like IL-1β, IL-6, and TNF-α, in the herb are able to reduce inflammation. Nonetheless, its ability to treat COVID-19 is not currently reported because the existing studies were conducted *in vitro* [23]. Moreover, there are not any uses of it in an extract or drinks for treatments.

Figure 2. The rhizome of *Boesenbergia rotunda* or finger root is the part most commonly used as a spice and herb.

Zingiber officinale: Ginger, shown in Figure 3, is a homegrown vegetable used in Thai recipes. Like finger root, it is spicy. Shogaol and Gingerol are important bioactive compounds found in it; they have antioxidants, as well as anti-inflammatory and antiviral effects [24]. *In silico* study found out that ginger extract might inhibit SARS-CoV-2 [25]. According to Thai traditional medicine, ginger aids digestion and relieves nausea and vomiting. There is no proof about its ability to fight against COVID-19; it is just suggested for healthy diets leading to strong immunity. It should not be used with anti-coagulant drugs. Moreover, patients with gallstones should not take it unless their physician recommends it. Children under 6 years old should avoid taking it because they might experience heartburn and an irritated mouth and neck. Those allergic to ginger might experience skin inflammation [24].

Figure 3. The rhizome of *Zingiber officinale* or ginger is the part most commonly used as a spice and herb.

Communication on Use of Herbs in COVID-19 outbreaks: Communication plays an important role in delivering knowledge to others. During the pandemic, it is critical for the healthcare system to advise citizens. In terms of the communication process, the Ministry of Public Health is considered a sender who initiates and conceptualizes the ideas. Their message about herbal medicines for treating COVID-19 is going to be conveyed to the reviewers, citizens, via various types of channels [26]. Fortunately, Thai citizens have been accustomed to the herbs for a long time, so they can more easily access the herbs than medicines. The herbs should be prescribed by the physicians for patients' safety. At the beginning, it was difficult to educate citizens about using accurate portions of herbs because traditional ways of using them (e.g., boiling in water) cannot control the amount of bioactive compounds present and cannot meet the Ministry of Public Health's recommendation. In addition, physicians initially lacked knowledge of the herbs. Consequently, most of them were concerned about drug interactions and adverse effects, such as

an increase in liver enzymes. As a result, the Ministry of Public Health has had to use KAP theory (Knowledge, Attitudes, and Practices) for creating a better communication [27]. It aims to provide accurate herbal knowledge (K) about safety, precaution, and availability. Furthermore, it would like to change attitudes (A) of health professions to be more open-minded about herbal treatments. Also, it is essential to change citizens' points of view about using herbs in incorrect traditional ways. The misconceptions have to be overcome because there is inadequate evidence to prove them. These lead to accurate practices (P). In order to achieve these goals, the Department of Thai Traditional and Alternative Medicine announced the procedure for herbal treatments of COVID-19 patients, and the Ministry of Public Health approved adding Fah Talai Jone to the Thai national list of essential medicines on 27th May, 2021. This caused herbs to attract a lot of attraction, resulting in a shortage of Fah Talai Jone. Nonetheless, there is still confusion about the quantity of andrographolide indicated in the labels, as each brand contains different amounts of andrographolide. Moreover, people are confused whether to use Fah Talai Jone powder instead of capsules; doing so will result in an under therapeutic drug level. Therefore, there should be further messages about Fah Talai Jone for citizens. The message should mention about Fah Talai Jone cannot prevent COVID-19 infection and using a high amount can cause liver problems.

On the internet, other herbs like ginger and finger root are believed to be used for treatment, without any reliable proof. Many consumers misunderstand and decide to wrongly buy herbal supplements to treat COVID-19. As a result, people should be informed that those herbs are not yet approved for their ability to reduce the severity of COVID-19. They should also be warned about their side effects and drug interactions when taken with certain drugs. Currently, the Ministry of Public Health just gives advice to use them for cooking, and waits for further clinical research about them.

CONCLUSION

Herbs serve as alternative management for pandemic diseases and allow patients to have more access to the treatments. The herbs should be selected carefully with reliable research about their safety and side effects. In Thailand, Fah Talai Jone is approved to be used while other herbs have only been researched in a test tube (*in vitro*) or are only recommended for cooking. During outbreaks, communication is one of the most important tools for educating citizens. Communications should be clear and continuous to ensure both citizens and health professionals accept the use of herbs for managing symptoms and health benefits. This will also encourage citizens to take good care of their health by consuming the herbs. In order to provide the information, it is crucial to do some clinical research to ensure that the information is correct and understandable for average citizens. However, there should be warnings about side effects, drug interactions, and *in vitro* research that might create some misconceptions in a society. Misconceptions might act as a barrier to understanding, which can lead to people improperly consuming herbs.

List of abbreviation: IL: Interleukin, IFN: Interferon, IC50: The half maximal inhibitory concentration, CC50: The 50% cytotoxic concentration

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