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Plant Solutions for the COVID-19 Pandemic and Beyond: Historical Reflections and Future Perspectives

As I write this commentary in late April 2020, the world is scrambling to cope with the COVID-19 pandemic. COVID-19, short for Coronavirus disease 2019, is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Globally, more than 3 million people have been infected by COVID-19 and over 200 000 people have died of this disease. Normal lives of billions of people around the world are disrupted. The global economic loss is incalculable. Where I am (Massachusetts, USA), universities have closed down since mid-March. Most researchers were sent to work from home, which means in-person lab research has to be abruptly halted. The COVID-19 pandemic ruthlessly deprives us of some of the very basic activities that we take for granted living in a modern society, such as going to work, eating out with friends, and attending social gatherings. As painful as it is, COVID-19 also serves as a wake-up call that reminds us how fragile our society still is when challenged by a pandemic, and much is to be learned about infectious diseases because we still lack effective ways to eradicate them.

Here, I reflect on the COVID-19 pandemic from the perspective of plant science. First, plants have served as the main source of medicine for humans since the beginning of our species. Some of the earliest modern medicines are indeed plant natural products for treating infectious diseases. Plants have a lot to offer for treating COVID-19 and other infectious diseases, but it will require interdisciplinary research efforts to fully realize this potential. Second, the countermeasures that were quickly deployed against COVID-19 this time, including disease detection and potential treatments, are resulted from previous science and technology development in broad disciplines. This strongly advocates for not just maintaining but significantly increasing societal funding into basic sciences, including plant science, in order to better prepare us for future pandemics and other societal challenges. Last but not least, the global COVID-19 crisis has exposed several weaknesses of human nature, and in many ways echoes other looming crises, such as climate change and food insecurity. Plant science could contribute to the solutions of these problems, but such effort needs to be integrated into a global grand strategy yet to be established.

THE HISTORY OF PLANTS AS MEDICINE FOR INFECTIOUS DISEASES

Infectious diseases have afflicted humans since hunter-gatherer days. When the agricultural revolution occurred around 10 000 years ago, the rise of densely populated communities greatly increased the chance of epidemics. Diseases such as malaria, tuberculosis, leprosy, influenza, and smallpox became known during that time. Through numerous trials and errors followed by extensive empirical exercises, indigenous people around the world have independently discovered a plethora of medicinal plants for treating various infectious diseases. For instance, in central Africa, *Ageratum conyzoides* (billygoat weed) was used to clear parasitic worm infection (Wabo Poné et al., 2011). A wide variety of medicinal plants were used for treating malaria; *Artemisia annua* (sweet wormwood) native to China and *Cinchona officinalis* (Cinchona tree) native to South America are the most well known (Mohammadi et al., 2020) (Figure 1A). In traditional Chinese medicine (TCM), elaborate multi-ingredient herbal remedies also emerged, most of which were indeed developed for treating infectious diseases, the primary cause of ailments in ancient times. As a prominent example, *Treatise on Cold Pathogenic and Miscellaneous Diseases*, regarded as a crown jewel among ancient TCM texts, was written by Zhang Zhongjing (AD 150–219) during the late Eastern Han dynasty when continuous wars and multi-year pandemics caused great human suffering and death (Figure 1B). Using a dialectic approach, Zhang Zhongjing systematically documented 113 herbal formulae and 397 therapeutic strategies for treating illnesses that were meticulously categorized by their differential disease manifestations and responses to alternative initial investigative treatments. The *Treatise* has since served as a cornerstone for TCM over the following two millennia.

The age of exploration led by Europeans starting in the 15th century inevitably spread many infectious diseases globally. Without previous exposure, as many as 90% of the indigenous people inhabiting North and South America perished due to smallpox, measles, and bubonic plague among other infectious diseases brought by Europeans. Upon arrival at new continents, colonists encountered many indigenous medicinal plants, which they then introduced back to Europe and other parts of the old world through trade. For instance, the miraculous antimalarial property of Cinchona tree bark was rediscovered by Spanish settlers in Peru in the mid-17th century. In the following years, Cinchona tree bark quickly became a highly prized medicine and was traded globally. Driven by curiosity and the need to deter species adulteration in medicinal plant trade, the field of plant systematics flourished. This culminated in the publication of *Species Plantarum* by Carl Linnaeus in 1753, which established the foundation of plant taxonomy as we know it today. In addition, the growing interest in medicinal botany prompted the origins of botanical gardens in several European countries, so that plants brought

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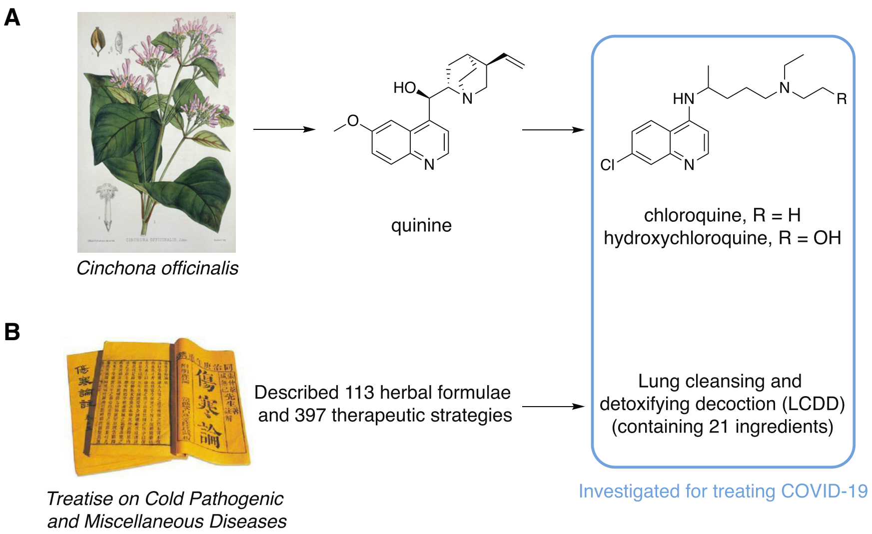

Figure 1. Two Examples of Plant-Derived Medicines Currently under Investigation for COVID-19 Treatment.

(A) Quinine was discovered as the principal bioactive compound from *Cinchona officinalis*, a South American antimalarial medicinal plant. Chloroquine and hydroxychloroquine are synthetic analogs of quinine and have been approved for treating malaria, HIV, systemic lupus erythematosus, and rheumatoid arthritis.

(B) The lung cleansing and detoxifying decoction (LCDD) widely used in treating COVID-19 patients in China was developed based on four formulae described in the classic TCM text *Treatise on Cold Pathogenic and Miscellaneous Diseases* by Zhang Zhongjing (AD 150–219).

back by colonists from all over the world could be cultivated and studied. Long-distance maritime voyages also caused health problems, such as scurvy, a common disease among sailors in the British Navy in the 18th century, manifested by deteriorating connective tissue. To find a cure for scurvy, James Lind, a naval physician, ran the first reported, controlled clinical trial in the history of medicine on the ship HMS *Salisbury* in 1747, and found citrus fruit to be an effective cure for scurvy. The rapid advances in medicinal botany and medical sciences for diseases during this period in turn protected the health of colonists when they continued to explore distant territories, contributing to the establishment of many colonial empires by the 19th century.

The mysteries behind many medicinal plants were ultimately resolved in the last two centuries when modern science took off. Quinine was isolated from Cinchona tree bark by the French chemists Pierre-Joseph Pelletier and Joseph-Bienaimé Caventou in 1820 with its chemical structure fully resolved a century later (Hoffmann, 2018) (Figure 1A). Quinine and its synthetic analogs became some of the earliest modern medicines for treating various diseases. Vitamin C, chemically named as L-ascorbic acid in honor of its activity against scurvy, was discovered collectively by the Hungarian biochemist Albert Szent-Györgyi and the British chemist Norman Haworth in the 1920s and 1930s. Inspired by an antimalarial remedy documented in the ancient TCM text *Prescriptions for Emergencies* authored by Ge Hong (AD 284–346), Chinese phytochemist Tu Youyou identified artemisinin from sweet wormwood in the 1970s, which led to the development of a new antimalarial medicine that saved millions of lives. Using a modern chemical biology approach, the action mechanism of artemisinin was recently elucidated, which entails activation of the signature endoperoxide bridge of artemisinin by heme iron enriched in the *Plasmodium falciparum* parasite to form highly reactive radicals that in turn bind to numerous target proteins (Wang et al., 2015). Medicinal plants have not only guarded human health against infectious diseases over millennia but also played an important role in the modernization and globalization of human society in recent centuries. As our scientific knowledge about plants grows, there is no doubt that we will continue to discover new plant-derived medicines.

PLANT-DERIVED MEDICINES CURRENTLY INVESTIGATED FOR COVID-19 TREATMENT

Similar to several other pandemics in recent decades, COVID-19 emerged as a new disease, and currently there is no effective medicine to eliminate SARS-CoV-2. Since a new drug discovery program can easily take more than 10 years with a high probability of failure, finding cures for COVID-19 to meet urgent need through this route seems unattainable. Numerous investigational drugs that have recently entered clinical trials for COVID-19 are all repositioned from molecules previously approved or under investigation for other indications (www.ClinicalTrials.gov). A preliminary clinical study in France recently showed promising results of chloroquine and hydroxychloroquine in reducing the SARS-CoV-2 viral load in COVID-19 patients (Gautret et al., 2020). Interestingly, chloroquine and hydroxychloroquine are synthetic analogs of quinine (Figure 1A), and have previously been repurposed for treating HIV, systemic lupus erythematosus, and rheumatoid arthritis, in addition to their antimalarial use. Studies of the quinine scaffold showed that this class of molecules has the unique property to enrich in lysosome, which underpins their antimalarial and antiviral activities. Multiple clinical trials using chloroquine and hydroxychloroquine to treat COVID-19 are currently ongoing (www.ClinicalTrials.gov).

In China, TCM has played an important role in the battle against COVID-19. In late January 2020, the National Administration of Traditional Chinese Medicine (NATCM) organized an urgent study section to identify effective prescriptions of TCM for prevention and treatment of COVID-19. Based on symptoms observed in early COVID-19 patients, several TCM formulae were developed, among which the lung cleansing and detoxifying decoction (LCDD) was one of the most widely used, and clinically studied. LCDD is a combined formula developed based on four classical formulae described in the *Treatise on Cold Pathogenic and*

Miscellaneous Diseases, and contains 21 ingredients: *Ephedra sinica*, *Cinnamomum cassia* (twig), *Alisma plantago-aquatica*, *Atractylodes macrocephala*, *Bupleurum chinense*, *Scutellaria baicalensis*, *Pinellia ternate* (pretreated with ginger and potassium alum), *Aster tataricus*, *Tussilago farfara*, *Iris domestica*, *Asarum sieboldii*, *Dioscorea polystachya*, *Agastache rugosa*, *Citrus aurantium* (dried young fruit), licorice (roasted), *Prunus armeniaca* (apricot kernel), ginger, orange peel, *Wolfiporia extensa*, *Polyporus umbellatus* and gypsum ($CaSO_4 \cdot 2H_2O$) (Figure 1B). According to a press conference held by the Joint Prevention and Control Mechanism of the State Council of China on April 17, the initial trial indicated that LCDD was effective on 90% of the 214 enrolled COVID-19 patients. Another trial with additional 1262 patients, including 57 with severe symptoms, showed that 99.28% of these patients have recovered by now and none with mild symptoms developed severe symptoms under LCDD treatment (http://www.gov.cn/xinwen/gwylflkjz95/index.htm [in Chinese]). Although these trial data are yet to be officially published, NATCM has officially recommended LCDD as a treatment for COVID-19. LCDD has since been widely used in 28 provinces and municipalities and has contributed to the relatively low mortality rate among COVID-19 patients in China. Several Chinese patent medicines (e.g., Lianhua Qingwen capsules) were also used for treating COVID-19 patients with many concomitant clinical observations currently ongoing. This topic has recently been well reviewed by Zhang et al. (2020) and is not discussed in detail here.

HOW TO FULLY UNLEASH THE MEDICINAL PROPERTIES OF PLANTS?

The chemical composition of LCDD is complex; control of consistent quality of a herbal remedy is challenging; and its action mechanism in treating COVID-19 is unknown. Previous research on individual ingredients and their principal bioactive compounds has shed some light. For instance, sesquiterpene atractylon and its analogs isolated from *Atractylodes macrocephala* show antiviral activities against H1N1 and H3N2 influenza viruses in cell-based assays, whereas *Atractylodes* root extract attenuated influenza A virus (IAV)-induced pulmonary injury in mice (Cheng et al., 2016). Ephedrine and pseudoephedrine, the principal bioactive compounds of *Ephedra sinica*, are clinically approved decongestants and bronchodilators (Abourashed et al., 2003). *Scutellaria baicalensis* produces baicalein and several related flavonoids, which are anti-inflammatory agents acting upon the NF-κB pathway (Hsieh et al., 2007). In a recent preprint, baicalein was found to be a potent inhibitor of the main protease of SARS-CoV-2, 3C-like protease, which could suppress the replication of SARS-CoV-2 in Vero cells (Liu et al., 2020). The cyclopeptide Astin C from *Aster tataricus* was recently found to specifically inhibit the innate immune cytosolic DNA sensor STING and thus modulates the STING-mediated immune response (Li et al., 2018). Licorice, *Dioscorea polystachya*, *Wolfiporia extensa*, and *Polyporus umbellatus* are rich sources of triterpenes, many of which harbor antiviral activities and/or act as steroidal hormone mimetics to modulate the mammalian immune system (Ríos, 2010; Khwaza et al., 2018). The combination of these activities likely counter COVID-19 by simultaneously inhibiting viral propagation, easing the symptoms of pneumonia, and suppressing the viral infection-induced cytokine storm. Unfortunately, the success of LCDD in China cannot be easily transferred to other countries for several reasons. First, the entire TCM infrastructure and the general cultural acceptance of TCM in China are lacking outside China. Hence, there is no mechanism for herbal remedies like LCDD to quickly enter clinics for treating COVID-19 as an investigational therapy or complementary medicine in the United States for example. Second, although the US Food and Drug Administration (FDA) has a route for botanical drugs to obtain approval through clinical trials, due to practical challenges such as patent protection, drug sourcing, and market acceptance, few sponsors have taken herbal remedies through FDA-guided clinical trials. Third, herbal remedies in their current form with largely unknown chemical composition and action mechanism fall below the high standard required for modern medicines. This results in low patient and physician acceptance, even though the safety and effectiveness of a given herbal remedy could be established clinically.

To solve this dilemma in the short term, countries wanting to test herbal remedies as potential therapies for COVID-19 need to reform their existing regulatory policies to facilitate and incentivize sponsors to run their own clinical trials. However, to fully unleash the medicinal power of plants to treat human diseases globally, a significant amount of interdisciplinary research is needed to study the genetics, chemistry, and biochemistry of diverse medicinal plants, develop capabilities of producing bioactive plant natural products and their analogs at will through metabolic engineering, and elucidate their action mechanisms and potential synergistic effects when used in combination (Li and Weng, 2017). Future generations of TCM-inspired modern medicines should contain single or combined bioactive plant natural products with known composition and action mechanisms and show equivalent or superior safety and efficacy when compared with traditional herbal remedies. Moreover, to preserve and research the world biodiversity of medicinal plants, agencies such as the World Health Organization could play a role to help establish a framework under which all regions of the world could gain access to funding and expertise to study their own medicinal plants and exchange their knowledge with the rest of the world.

THE COVID-19 PANDEMIC CALLS FOR A SIGNIFICANT INCREASE IN SOCIETAL FUNDING INTO SCIENCE

Scientifically, we were in a better position than ever before when COVID-19 hit. Scientists were able to quickly identify the disease-causing virus, sequence its genome, and develop various methods of disease diagnosis. Within months, a multitude of prevention and treatment strategies were devised, many of which were put into practice. This is a strong testament for the paramount importance of science to the future well-being of humans. Without prior research investment in areas such as virology, genomics, immunology, chemistry, and CRISPR technology, we would not have the tools or the scientific workforce to battle against COVID-19. Without pharmaceutical industry's previous efforts to find cures for other diseases, we would not have the list of investigational drugs and vaccines to quickly enter clinical trials targeting COVID-19. Unfortunately, the pre-COVID-19 world did not seem to value science enough, despite its purported importance. In the United States, for example, the total federal budget for major science funding agencies, including the National Institutes of Health (NIH), the National Science Foundation (NSF), and the Department of Energy (DOE), has been miniscule compared with its annual defense budget in past decades. For this year, deep cuts in federal research spending were also proposed (Mervis, 2020). Had we invested more in science, for instance in the underfunded area of infectious diseases, we probably would have a few more tools in hand to fight against COVID-19, hence reducing its toll on society. Research projects to study medicinal plants with antiviral properties, for which funding was difficult to obtain in the pre-COVID-19 climate, might have yielded potential cures for COVID-19. Even for the seemingly distantly related field of plant engineering, clever heterologous expression systems in plants might well be adapted to produce vaccines or therapeutic antibodies.

We have now painfully learned that a global public health crisis like COVID-19 in the 21st century can cost society even more than a regional war. Our inability to eradicate COVID-19 is due to our ignorance about the disease and lack of technological capabilities to dismantle it, both of which can be solved by science. In a post-COVID-19 world, societal funding into science should be significantly increased to better prepare us for future societal challenges like COVID-19. It is important that diverse scientific disciplines should be funded, because it is impossible to predict what the next challenge will be and what scientific solutions will be needed to address it. Given the significant contributions that plant science has made to societal advancement in human history, increasing funding into plant science will be critical and totally worth it.

COVID-19 TEACHES US AN INVALUABLE LESSON ON HOW TO ADDRESS OTHER GLOBAL CHALLENGES

The COVID-19 pandemic exposes several weaknesses of human nature. The unwillingness to take inconvenient near-term preventative measures to avert predictable long-term crises have hurt some countries during this pandemic. Moreover, when disasters hit, the tribalism nature of humans gets amplified, which hampers our species' unique strength of collaborating with each other. This is the exact opposite of what we need right now to defeat the virus. Although COVID-19 is already bad enough, I can't help thinking about other looming crises of a similar nature. For example, we are currently on a trajectory toward continued increase in atmospheric CO_2 concentration, global climate change, sea level rise, and ultimately, environmental and socioeconomic catastrophes. Unlike COVID-19, which will fade away in the coming months to years, the curve of the increase in atmospheric CO_2 concentration cannot be easily flattened, and the consequences will stay with us for a much longer term (National Academies of Sciences, 2019). The COVID-19 pandemic also sounded the alarm for food insecurity. Temporary interruptions to the global food supply chain due to geopolitical reasons or a pandemic like COVID-19 put food security at instant risk. In the long term, overpopulation, diminishing arable land, and loss of plant productivity caused by climate change have been forecasting significant global food supply shortfalls compared with demand in the future.

As a society, we must learn from where we succeeded and failed in dealing with the COVID-19 pandemic and take these lessons to heart when addressing other global challenges facing mankind. Again, plant science is well poised to make important contributions to these challenges. Plants are primary sequesters of atmospheric CO_2 on Earth, using only sunlight as the energy input. For instance, engineering plants to accumulate inert carbon-trapping polymers such as suberin and sporopollenin can help rebalance the global carbon cycle. Developing crops with enhanced productivity, disease resistance, and abilities to withstand harsh environmental conditions will be critical to ensure future sustainability of humans on Earth. However, we need comprehensive collaborations at a global scale to integrate plant biotechnologies with other technologies and policies to create grand actionable mitigation strategies. As scientists around the world work collectively to defeat COVID-19, sharing their results with unprecedented transparency and speed, I see hope that united as one human race, we will overcome the challenges lying ahead.

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